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**The impact of health care professional training on
adolescent hay fever: cluster randomised controlled trial of
a complex intervention in primary care**

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Thesis presented in fulfilment of the requirement of the degree
of Doctor of Philosophy

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Declaration

I hereby declare that this thesis was composed by me and is entirely my own work.

It has not been submitted for any other degree or professional qualification.

Victoria Hammersley

2014

Abstract

Background

Hay fever is typically poorly managed, particularly in adolescents, in whom it is responsible for considerable morbidity and impairment in educational performance. Evidence-based training of professionals has the potential to improve outcomes, but it can be expensive and so warrants formal evaluation. This trial sought to evaluate the effectiveness of a training intervention for primary care-based health care professionals on adolescent disease-specific quality of life.

Methods

A cluster randomised controlled trial was conducted in UK general practices. Practices were centrally randomised to a short, intensive training course on the evidence-based management of hay fever (intervention arm) or distribution of guidelines (control arm). The primary outcome measure was the change in the validated Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S)) score in adolescents with hay fever between baseline and six weeks post-intervention (minimal clinically important difference = 0.5). Secondary outcome measures included health care professionals' knowledge and confidence in managing hay fever, number of hay fever-related consultations, relevant treatments prescribed and symptom scores. Multi-level modelling using a random effects model was used to take account of between and within cluster variation, adjusting for strata, individual covariates and year of study.

Results

Thirty-eight general practices were randomised (20 in the intervention arm) and 246/341 patients (50.2% male, mean age 15 years) were included in the primary outcome analysis. Health care professionals' self-assessed knowledge and confidence improved (prescribing/recommending treatment mean score 95% CI 1.4, 2.8), and the training was perceived to be of value. This did not however result in clinically or statistically significant improvements in RQLQ(S): -0.15, 95% CI -0.52 to +0.21. There were no differences in consultation frequency (95% CI -0.02, +0.63), treatments issued for hay fever (95% CI -0.24, +0.08) or symptom scores (95% CI -1.03, +0.54).

Conclusions

Although attendance on this short, intensive hay fever training course was associated with professionals' increased self-assessed confidence and understanding of the clinical management of hay fever, this did not translate into improvements in disease-specific quality of life or reduction in rhinitis symptoms in adolescents with hay fever.

Dedication

For my family

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Contributions to science

- **Hammersley V**, Elton R, Walker S, Hansen C, Sheikh A. Adolescent hay fever and the impact of healthcare professional training: a cluster randomized controlled trial in primary care. *npj Primary Care Respiratory Medicine* 2014; **24**, Article number: 14012
- **Hammersley V**, Flint R, Pinnock H, Sheikh A. Developing and testing search strategies to identify patients with active seasonal allergic rhinitis in general practice. *Primary Care Respiratory Journal* 2011;20:71-4.
- **Hammersley V**, Elton R, Walker S, Sheikh A. Protocol for the adolescent hay fever trial: cluster randomised controlled trial of an educational intervention for health care professionals for the management of school-age children with hay fever. *Trials* 2010;11:84.
- **Hammersley V**, Walker S, Sheikh A. Is it unfair to hay fever sufferers to have to sit examinations during periods of high pollen counts? *Expert Review Respiratory Medicine* 2010;4:421-5.
- **Hammersley VS**, Sheikh A. Early life infections and the risk of hay fever. *Primary Care Respiratory Journal* 2008;17:194.
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- Sheikh A, Walker S, **Hammersley V**, Shehata Y. Allergic rhinitis. *Scottish Primary Care* 2007;62:8-9.

Abbreviations

ARIA	Allergic Rhinitis and its Impact on Asthma
BSACI	British Society for Allergy and Clinical Immunology
CONSORT	Consolidated Standards of Reporting Trials
GCSE	General Certificate of Secondary Education
GP	General Practitioner
ICC	Intra-cluster Correlation Coefficient
IgE	Immunoglobulin E
IMD	Index of Multiple Deprivation
ISAAC	The International Study of Asthma and Allergies in Childhood
ISD	Information Services Division
MAR	Missing at Random
MCAR	Missing Completely at Random
MCID	Minimal Clinically Important Difference
MNAR	Missing Not at Random
MRC	Medical Research Council
NHS	National Health Service
NPARU	National Pollen and Aerobiology Research Unit
NYREN	Northern and Yorkshire Research Network
pmg ³	Pollen grains per cubic metre
PROC MI	Multiple Imputation Procedure of SAS
QoL	Quality of Life
R&D	Research and Development
RCT	Randomised Controlled Trial
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire
RQLQ(S)	Standardised Rhinconjunctivitis Quality of Life Questionnaire
SAS	Statistical Analysis System
SIMD	Scottish Index of Multiple Deprivation

SMS	Short Message Service
SOA	Super Output Area
SPCRN	Scottish Primary Care Research Network
SPT	Skin prick testing
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

Chapter 1 – Introduction

This opening chapter introduces key concepts in relation to allergic disorders with particular reference to hay fever. The current definitions of allergic disorders and how these evolved over time are reviewed, moving on to discuss the epidemiology and disease burden associated with hay fever. Existing evidence-based treatment guidelines for primary care, shortcomings in the provision of care, and the need for educational interventions for primary-care based health professionals are considered in relation to the development of the intervention used in the cluster randomised controlled trial.

1.1. Allergy

The term allergy was introduced first proposed by Clemens von Pirquet in 1906 (von Pirquet 1906) and was generally understood to describe the concept of altered biological reactivity to an antigen, which he defined as a foreign substance which could be either protective (offering immunity) or allergenic (harmful) (Kay 2001). This term is however sometimes now used in a more restrictive sense so it is synonymous with IgE-mediated disorders, these including, for example, allergic rhinitis and subsets of asthma and anaphylaxis (Johansson et al. 2001).

1.2. Early descriptions of hay fever

Early references to clinical observations resembling modern day allergy appear as far back as the 2nd century AD (Emanuel 1988), however no descriptions of hay fever-like symptoms appear before about the 16th century. Reference to ‘smelling roses and symptoms of headache, sneezing and troublesome itching of the nose’ dating from the middle of the 16th century are described in a monograph entitled ‘Hayfever, its

etiology and treatment’ by Sir Morell Mackenzie in 1884. The expression ‘hayfever’ was coined in the 1800s by John Bostock, who in 1819 theorised that the symptoms were caused by the fumes and, therefore, heat from hay. In this classic description of himself, Bostock describes all the afflictions we recognise as symptoms of hay fever today:

‘A general fullness is experienced in the head, and particularly about the fore part; to this succeeds irritation of the nose, producing sneezing, which occurs in fits of extreme violence, coming on at uncertain intervals’. (Bostock 1819)

It was 50 years later before the scientist Charles Blackley related his own symptoms to pollen by collecting and storing grass pollen until the winter months, when he inhaled the pollen and noted an acute reaction of streaming eyes, running nose and sneezing (Sheikh et al. 2013). In the 19th century, hay fever became more common in Europe and North America, a rise which has been closely associated with post-Industrial Revolution urbanisation, which brought about changes in agricultural practice, population movements and a very different way of life for much of the population (Emanuel 1988).

1.3. Definitions and classification of rhinitis

Allergic rhinitis has been defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes of the nose (Scadding et al. 2007). It is characterised clinically by symptoms such as rhinorrhoea, sneezing, nasal blockage and itching of the nose (Greiner et al. 2011) which are reversible, either spontaneously or with treatment; current definitions suggest that these symptoms need to occur during two or more consecutive days (Bousquet et al. 2008). Rhinitis can be classified into non-allergic and allergic;

allergic rhinitis can further be divided into intermittent or persistent (Bousquet, Khaltaev et al. 2008). There are several causes of non-infectious rhinitis and of these allergic rhinitis is the most common. Table 1.1 summarises the various causes of rhinitis.

Table 1.1: Classification of rhinitis (from ARIA 2008 update (Bousquet, Khaltaev et al. 2008))

Classification	Type/Cause
Allergic	Intermittent Persistent
Infectious	Viral Bacterial Other infectious agents
Occupational	Intermittent Persistent
Drug induced	Aspirin Other medications
Hormonal	e.g. during pregnancy or menopause
Other causes	Non-allergic rhinitis with eosinophilia (NARES) Irritants Food Emotional Atrophic
Idiopathic	

Allergic rhinitis was previously classified on the basis of time of exposure and duration of symptoms into seasonal or perennial (International Rhinitis Management Working Group 1994), depending on sensitisation to seasonal tree, grass and weed pollens and mould spores, or allergens which are present all year round such as house dust mites and animal dander. This classification system was thought unhelpful globally, as many countries do not have distinct seasons, pollens and moulds are perennial in some areas, and symptoms of perennial rhinitis may not be present all year round depending on allergen exposure. The classification system was therefore

revised in the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline (Bousquet, Khaltaev et al. 2008) to one based on the frequency and severity of symptoms and shown in Table 1.2.

Table 1.2: Classification of allergic rhinitis according to ARIA (adapted from ARIA 2008 (Bousquet, Khaltaev et al. 2008))

<p>Intermittent symptoms</p> <ul style="list-style-type: none"> • Less than four days a week or • Less than four consecutive weeks 	<p>Persistent symptoms</p> <ul style="list-style-type: none"> • More than four days a week and • More than four consecutive weeks
<p>Mild</p> <ul style="list-style-type: none"> • Normal sleep • Normal daily activities • Normal work and school • Symptoms present but not troublesome 	<p>Moderate to severe (one or more present)</p> <ul style="list-style-type: none"> • Sleep disturbance • Impairment of daily activity, leisure, sport • Impairment of school or work • Troublesome symptoms

1.3.1. Nomenclature used in this thesis

The terms seasonal and perennial cannot be used interchangeably with intermittent and persistent, as they do not represent the same stratum of disease (Bousquet, Khaltaev et al. 2008). However, in Western Europe, tree and grass pollens are the most important aeroallergens leading to allergic symptoms in the spring and summer and therefore the terms seasonal allergic rhinitis as well as intermittent rhinitis or even allergic rhinitis are commonly used in the literature. When reporting directly from the literature the term referred to by the authors will be used, however, for the purposes of the patients described in the trial reported in my thesis, the term hay fever will be used for intermittent allergic rhinitis as the seasonality is clear in the

United Kingdom (UK) (Scadding et al. 2008), with most general practitioners still using the code for seasonal allergic rhinitis/hay fever in patient electronic medical records for diagnosis (Hammersley et al. 2011).

1.4. Biological mechanisms of allergic rhinitis

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure, which results in immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose (World Health Organization Initiative et al. 2001). Coombs and Gell (1963) proposed a classification of four different reaction patterns for allergic reactions; allergic rhinitis is, using the classification system, a clinical example of Type 1 Immediate Hypersensitivity. Exposure to the allergen leads to cross-linking of membrane bound IgE on mast cells and/or basophils, which in turn causes a release of immediate mediators such as histamine and the formation of prostaglandins and leukotrienes and synthesis of cytokines, which further amplify the reaction (Roeken et al. 2003). The immediate response to mediator release will be nasal itching, sneezing, rhinorrhoea and congestion of the nose. When allergen levels are high or contact continues, a late phase response involving cellular inflammatory infiltrates such as eosinophils can lead to chronic ongoing rhinitis symptoms, such as nasal blockage and nasal hyper-reactivity (Scadding 2008).

1.5. Prevalence of allergic diseases

Allergy is one of the most common chronic diseases and affects up to 50% of the UK paediatric population at some point in their lives (Punekar et al. 2009). The world-wide prevalence of respiratory allergies has dramatically increased in the past 50 years (Asher et al. 2006; Bjorksten et al. 2008) and in the last decade food allergy has emerged as the second wave of the allergy epidemic (Prescott et al. 2011).

Atopic eczema/dermatitis is estimated to affect one in three children under 18 years, one in five with asthma and one in 10 with rhinitis (Punekar and Sheikh 2009). There is some evidence from time trend analysis of existing datasets and surveys that the prevalence of hay fever may be stabilising (Gupta et al. 2007). More recent evidence of atopic eczema/dermatitis incidence and prevalence showed no clear global trend; however, prevalence appears to be increasing in western Europe and parts of northern Europe, including the UK (Deckers et al. 2012). In addition to these high levels of individual disease prevalence, multiple allergic conditions often co-exist, figures of up to 16% of children under 18 years have been found to have more than one allergic disease (Punekar and Sheikh 2009; Punekar et al. 2009) which may partly be explained by the concept of the atopic march, which describes the progression of atopic disorders from atopic dermatitis in infants to allergic rhinitis and asthma in children (Spergel et al. 2003).

1.6. Epidemiology of allergic rhinitis

Allergic rhinitis is a global health problem affecting males and females of all ages from all ethnic groups and socioeconomic backgrounds (Baldacci et al. 2012). One of the most common allergic problems in young people is allergic rhinitis, affecting up to 40% of 13-14 year olds; this is closely followed by asthma which affects about 30% of young people (International Study of Asthma and Allergies in Childhood 1998). There are many national and international studies describing the prevalence of allergic rhinitis and its risk factors (Bousquet, Khaltaev et al. 2008): the International Study on Asthma and Allergy in Childhood (International Study of Asthma and Allergies in Childhood 1998) (ISAAC) specifically aimed to describe the prevalence and severity of asthma, rhinitis and atopic eczema/dermatitis in children living in

different countries and to make comparisons within and between these countries. Phase 3 of the study was planned to assess time trends in the prevalence of symptoms by repeating the cross-sectional survey from Phase 1 after at least five years. Most centres showed a change in the prevalence of symptoms of allergic rhinoconjunctivitis for the age-groups 6-7 years and 13-14 years (80% and 70% respectively), and in both cases the prevalence increased more often than it decreased for all levels of mean prevalence (Asher, Montefort et al. 2006). Data from all centres combined showed that the proportion of children with symptoms of more than one of asthma, allergic rhinoconjunctivitis and atopic eczema/dermatitis rose slightly from Phase 1 to Phase 3.

1.6.1. Social and economic burden of allergic rhinitis

Allergic rhinitis causes major illness and disability worldwide (Bousquet, Khaltaev et al. 2008). It is known to impact on how patients function in day-to-day life. Loss of sleep, inability to concentrate and risk of developing a major depressive disorder are common, and all impact quality of life (Blaiss et al. 2004). Work and school performance (Juniper et al. 1994; Walker et al. 2007) are known to be affected, particularly in patients with moderate/severe symptoms. Studies have shown that adults with allergic rhinitis experience a reduction in cognitive function and psychological well-being (Kremer et al. 2002), and that children with symptomatic allergic rhinitis had significant learning impairment in a simulated educational setting compared with asymptomatic controls (Vuurman et al. 1993). This detrimental effect has been shown to be compounded by the use of sedating H1-antihistamines (Vuurman et al. 1996). A more recent study has shown that when compared with healthy controls, allergic rhinitis sufferers experience increased

difficulty with tasks requiring sustained attention (Hartgerink-Lutgens et al. 2009). Most of the economic analyses to date are based on American populations; in 2003 the estimated annual costs of allergic rhinitis range from \$2 to \$5 billion (Blaiss 2007). These estimates include indirect costs such as reduction in productivity, which are difficult to predict. In the UK, direct National Health Service (NHS) costs for managing allergic problems were estimated at over £1 billion per annum (Gupta et al. 2004).

1.6.2. Measuring the impact of allergic rhinitis on quality of life

It is widely recognised that allergic rhinitis comprises more than the classical symptoms such as sneezing and rhinorrhoea (Bousquet, Khaltaev et al. 2008). The term ‘quality of life’ (QoL) is difficult to define as it means many different things to different people. It can, for example, include spirituality, health and emotional status to name a few. Health related quality of life (HRQL) is a component of QoL that is determined primarily by the person’s health and that can be influenced by clinical interventions (Juniper 1997). It has been defined as ‘the functional effects of an illness and its consequent therapy upon a patient, as perceived by the patient’ (Schipper 1990). In the last 20 years, many health-related quality of life tools have been developed, some, but not all, using established principles of instrument development (Fitzpatrick et al. 1998). In selecting an appropriate evaluative instrument for the primary outcome measure of the proposed trial, only disease-specific validated quality of life tools for rhinoconjunctivitis were considered. Disease-specific quality of life tool are the instruments most widely used to measure quality of life because they more accurately describe the problems associated with the disease and are more responsive to possible alterations in the quality of life when

compared with generic tools (Camelo-Nunes et al. 2010). A systematic review of patient reported outcome measures (PROMS) for asthma and allergic diseases (Worth et al. 2012) identified 17 PROMS specifically relating to allergic rhinitis (Worth et al 2012 Unpublished report). Of these only three were quality of life tools. The QOL-RIQ (Quality of Life Respiratory Illness Questionnaire) (Maillé et al. 1997) was designed more specifically to measure breathing difficulties associated with conditions such as chronic obstructive pulmonary disease, and therefore was not considered appropriate for this trial. RhinoQOL was designed to measure quality of life of patients with sinusitis specifically (Atlas et al. 2005) rather than rhinoconjunctivitis, and therefore was not considered appropriate for this trial. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) was one of the first tools to be developed by Juniper et al in 1990 (Juniper et al. 1991) and it is a widely used and well validated QoL measure (Juniper, Guyatt et al. 1994; Juniper et al. 2002; Juniper et al. 2007; Sheikh et al. 2007). The RQLQ contains 28 items in seven domains: activity, sleep, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms and emotional function. A modification was applied to the activity domain of the RQLQ, which allows patients to select their own activities rather than select from a pre-specified list of activities, allowing the activity selected to remain specific for that patient throughout its use in trials. The RQLQ was initially tested for reproducibility, responsiveness and validity in a clinical trial of patients with perennial rhinitis, using a nasal symptom diary for comparison (Juniper et al. 1993). Results showed moderate correlations ($r = 0.3 - 0.5$) in all domains. The limitation of the RQLQ for use in this trial was the administration - it is recommended that initially an interviewer assists the patient to identify three

activities which are limited by their hay fever, and subsequently the RQLQ can be self-administered. This measure has been developed further into a standardised version (RQLQ(S)) (Juniper et al. 1999), where the three activity questions are replaced by standardised activities allowing self-administration, and this has been shown to have the same measurement properties and to measure the same construct as the RQLQ (Juniper, Thompson et al. 1999). Having identified the RQLQ as a disease specific quality of life tool which seemed the most appropriate for this trial, I visited Professor Elizabeth Juniper and discussed with her the range of tools she had developed. An adolescent RQLQ had been developed, but not widely validated at the time, and her advice was to use the standardised version of the RQLQ (RQLQ(S)) as it was well validated for use as a self-complete questionnaire which was necessary for this trial. Additionally this tool was potentially available for use electronically which would possibly appeal to the participants in the trial, however at the time the RQLQ(S) had not undergone validation in an electronic version, and Professor Juniper was not willing for this to be used in the trial until this exercise was complete, therefore paper versions were used.

The minimum clinical important difference (MCID) is defined as “the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient’s management” (Juniper et al. 1994). The MCID for the RQLQ has been estimated as 0.5 (Juniper et al. 1996); and a validation study of the RQLQ(S), which compared responsiveness and the MCID of the RQLQ and RQLQ(S) in 83 patients, showed very good responsiveness for both instruments and very similar MCIDs (Juniper et al. 1999).

1.6.3. Co-morbidity

Allergic rhinitis is linked to other inflammatory diseases affecting respiratory mucous membranes (Greiner, Hellings et al. 2011). In particular, allergic rhinitis and asthma frequently coexist, with population surveys estimating that up to 40% of all allergic rhinitis patients have asthma and that 80% of patients with asthma also have allergic rhinitis (Leynaert et al. 2000; Casale et al. 2004; Walker et al. 2005). Other co-morbidities include allergic conjunctivitis, allergic sinusitis and atopic eczema/dermatitis. Allergic rhinitis and asthma are highly prevalent conditions and cause substantial health and economic burden to the individual (Vandenplas et al. 2010), and the impairment of quality of life experienced by patients with rhinitis is at least as severe as that of patients with asthma (World Health Organization Initiative, Bousquet J et al. 2001).

1.7. Aetiology and risk factors

As discussed above, the symptoms of hay fever are caused by an IgE-mediated type 1 hypersensitivity reaction to grass, tree, or weed pollens. Allergy to other seasonal aeroallergens such as fungal spores may also provoke symptoms. Seasonal allergic conjunctivitis results in eye itching and watering and is often associated with allergic rhinitis, commonly in children and young adults sensitised to tree or grass pollen. Typically, symptoms become worse during the relevant pollen season, and outdoors when pollen exposure is increased. Risk factors include a personal or family history of atopy or other allergic disorders, high socioeconomic status (Jones 2004), birth order (Strachan 1989) (increased risk being seen in first born), and small family size (Greiner, Hellings et al. 2011).

1.7.1. Measuring pollen counts

Sites throughout the UK report daily pollen counts for the most allergenic pollens such as grass, birch, oak and nettle, however, over 90% of hay fever sufferers are affected mainly by grass pollen in temperate regions (Emberlin 1997). The grass pollen season can vary from year to year because of its onset, total seasonal cumulative count and severity in terms of the number of days with high counts, and this can be attributed to weather variations and environmental factors (Emberlin et al. 1999). This is important in considering the timing of prophylactic pharmacotherapy. At the time of this trial, pollen data were collected and collated by the National Pollen and Aerobiology Research Unit (NPARU) at the University of Worcester (<http://www.worcester.ac.uk/discover/national-pollen-and-aerobiology-research-unit.html>). The pollen count is a measure of the number of pollen grains of a certain type per cubic metre of air sampled, averaged over 24 hours. Pollen monitoring sites around the UK have a Burkard volumetric spore trap. These are usually located on the roof of a suitably accessible building to enable the ambient airflow to be monitored. This generally catches a good mix of local and distant pollen sources carried by the wind.

1.8. Diagnosis and investigations

A number of diagnostic tests are available to confirm a diagnosis of allergic rhinitis. A clinical assessment and evidence of an aero-allergen trigger is generally sufficient to make a diagnosis in the case of hay fever (Walker et al. 2006), however a study comparing a structured allergy history and skin prick testing (SPT) with patient's self-report, or a structured allergy history alone, showed that combining a structured allergy history and SPT improved the accuracy of an assessment of allergic status

(Smith et al. 2009). Specific IgE reactivity to relevant aeroallergens can be measured either by SPT or measuring IgE in serum samples. Skin prick testing involves introducing a very small drop of purified allergen extract into the skin, which is punctured by a 1mm lancet. The aeroallergens chosen for an allergic rhinitis diagnosis are usually mixed grass and tree pollen, any other aeroallergens suggested by the presenting history, plus a positive and negative control. After 10-15 minutes, any resulting wheal and flare response is recorded as the mean of a vertical and horizontal diameter, and generally a reaction with a mean diameter 3mm bigger than the negative control is considered to be positive (EAACI Subcommittee 1993). Although skin prick testing of aeroallergens is considered to be safe, very little testing is carried out in primary care (Smith, Hogger et al. 2009). High serum IgE concentrations can be indicative of IgE-mediated disease, however there is overlap between atopic and non-atopic ranges (Burney et al. 1997) and this test is of limited use. Laboratory allergen specific IgE tests such as ImmunoCAP (Phadia, Uppsala, Sweden) are available but not routinely used for allergic rhinitis diagnosis confirmation (Walker, Morton et al. 2006).

1.9. Management and treatment

The aim of treatment for people with allergic rhinitis is to achieve safe and effective relief from symptoms; a multi-faceted approach may therefore contain patient education, minimisation of allergen contact, pharmacotherapy and consideration of immunotherapy (Greiner, Hellings et al. 2011). Recommendations in the British Society for Allergy and Clinical Immunology Guidelines for the treatment of allergic rhinitis (Scadding, Durham et al. 2008) are presented with a grade of recommendation based on the reviewed literature. For example, topical nasal

corticosteroids are considered to be the treatment of choice for moderate to severe disease (Grade of recommendation A). Consideration of alternative approaches to pharmacotherapy such as allergen avoidance suggests little evidence for their effectiveness (Greiner, Hellings et al. 2011). Concordance with any prolonged treatment regime is crucial, and education about the disease and mode of application and safety of treatment are vital to achieve this (Scadding 2008).

The principle treatment options for managing allergic conditions are:

- Allergen avoidance
- Pharmacotherapy
- Immunotherapy

These are briefly considered below.

1.9.1. Allergen avoidance

Allergen avoidance is recommended, where possible and appropriate, as first-line treatment for managing allergic conditions, and it is therefore important to identify the allergen and give advice on practical strategies for allergen avoidance. In patients suffering from intermittent symptoms, exposure to grass or tree pollens are the most common trigger. Tree pollens are particularly prevalent in the spring (February to May) and grass pollens in the early summer (May to July). Although complete allergen avoidance is practically impossible to achieve, obvious measures such as closing windows in the early evening, avoiding grass cutting and outdoor activity when pollen counts are high are simple and may help some people, although there is little scientific evidence to support this. Accurate identification of the pollen/allergen using objective allergy tests such as skin prick tests, detection of serum specific IgE

and nasal provocation challenge testing may help to advise patients when to take prophylactic allergic rhinitis treatment (Sheikh et al. 2005; Shehata et al. 2007).

1.9.2. Pharmacotherapy

A systematic review of the RCT literature on the effectiveness of common pharmacological treatment used in hay fever in people aged 12 (Sheikh et al. 2009) and over is summarised in Table 1.3. These treatments aim to minimise or eliminate symptoms, optimise QOL, and reduce the risk of developing co-morbidity.

Table 1.3: Treatment for hay fever (from Clinical Evidence 2009;10:509)

Treatments of hay fever

Beneficial

- Intranasal antihistamines (e.g. azalestine)
- Intranasal corticosteroids
- Oral antihistamines (acrivastine, azatadine, brompheniramine, cetirizine, levocetirizine, ebistine, fexofenadine, loratidine, destoratidine, rupatadine, and mizolastine)
- Oral antihistamine plus pseudoephedrine plus (reduces nasal symptom severity compared with antihistamines alone)

Likely to be beneficial

- Intranasal antihistamines (levocabastine and olopatadine)
- Leukotriene receptor antagonists (oral)
- Systemic corticosteroids

Unknown effectiveness

- Intranasal ipratropium bromide
- Oral decongestants

Unlikely to be beneficial

- Oral antihistamines plus leukotriene receptor antagonists (seem no more effective than either treatment alone)

Likely to be ineffective or harmful

- Oral antihistamines (astemizole and terfenadine; associated with cardiac adverse effects)

1.9.3. Immunotherapy

Allergen-specific immunotherapy involves administering gradually increasing quantities of an allergen extract to which an individual is sensitised, over a prolonged period of time. Treatment aims to induce clinical and immunological tolerance, has long-term efficacy and may prevent the progression of the disease (Bousquet, Khaltaev et al. 2008). Immunotherapy is most commonly administered as subcutaneous injections, but may also be delivered by the sublingual route (Walker et al. 2011). At present, immunotherapy is confined to use in specialist centres because of the risk of serious allergic reactions (Calderon et al. 2007), and is recommended in patients whose symptoms did not respond to adequate pharmacotherapy. Sublingual immunotherapy has been shown to be a safe treatment (Wilson et al. 2005; Walker, Durham et al. 2011), where only the first dose needs to be given under supervision.

1.10. Shortcomings of provision of allergy services in primary care

A report published in 2003 *Allergy – the unmet need*, commissioned by the Royal College of Physicians, clearly demonstrated current deficiencies in NHS allergy services in the UK, and made a number of proposals to improve patient care, both in primary and secondary care. In 2004, the House of Commons Select Committee on Health (Health Committee 2004) reported that ‘serious problems exist in the current provision of allergy services in the UK’, and ‘those working in primary care lack the training, expertise and incentives to deliver services’. These findings have been confirmed in relation to allergic rhinitis in a survey of general practitioners whose practice had a self-declared interest in the management of allergic and respiratory disorders (Ryan et al. 2005). There was considerable variation in the awareness and management of allergic rhinitis. In 2010, a follow-up report - *Allergy services – still*

not meeting the unmet need (Royal College of Physicians 2010) reported the continuing deficiencies in allergy service provision, and stated that there had been little progress in the governance and training of primary care providers who were managing allergic diseases.

The House of Lords Science and Technology Committee report on Allergy (House of Lords Science and Technology Committee 2006-7) recommended that the Department for Children, Families and Schools should review the clinical care that children receive at school, and should reassess the way they are supported through the examination season. However, the knowledge and training in allergic diseases of teachers and support staff may not be sufficient to support children through this period (House of Lords Science and Technology Committee 2006-7). Enhancing the role of primary care professionals in ensuring control of allergy symptoms by improving training and engaging the patient may be a more beneficial and safer approach.

1.11. Literature review of educational interventions in primary care

There are a broad range of interventions which aim to improve health care professional practice in primary care and these have been widely reported in a number of systematic reviews (Oxman et al. 1995; Freudenstein et al. 1999; Grimshaw et al. 2001; Wensing 2008). The interventions reviewed include different approaches to changing professional behaviour, which broadly fit the following strategies (Grimshaw, Shirran et al. 2001):

- Educational materials – distribution of published or printed recommendations for clinical care including clinical practice guidelines.

- Conferences – participation of health care providers in conferences, lectures, workshops or traineeships.
- Local consensus process – inclusion of participating providers in discussion of the clinical problem and solution to ensure it is appropriate locally.
- Educational outreach visits – use of a trained person who meets the providers in the health care setting to provide information with the aim of changing the provider's performance.
- Patient-mediated interventions: any intervention where specific information is sought from or given to patients, e.g. direct mailing to patients, educational materials given to patients.
- Audit and feedback – any summary of clinical performance given over time, e.g. average number of prescriptions given or tests ordered, which may also include a recommendation for clinical care.
- Reminders (manual or computerised) – a prompt that reminds the health care provider to perform a patient or encounter specific clinical action, e.g. measuring blood pressure annually.
- Marketing – use of personal interviewing, discussions groups or a survey of targeted providers to identify barriers to change.
- Multi-faceted interventions – any intervention that includes one or more of the above.

Grimshaw et al (2001) concluded that the more passive dissemination strategies such as mailing educational materials to targeted clinicians is generally ineffective when used alone to change behaviour, but may be helpful for raising awareness of the need

for change (Grimshaw, Shirran et al. 2001). Audit and feedback and the use of local opinion leaders had variable effectiveness, whilst strategies such as educational outreach and reminders were reported to be generally effective. The evidence specifically from primary care interventions is variable. A review of the evidence of the effectiveness of educational interventions for GPs for health outcomes for patients with asthma (Barton et al. 2003) identified three RCTs where the educational intervention included health professional education and the effects of the intervention on patient health outcomes were reported (White et al. 1989; Smeele et al. 1999; Clark et al. 2000). Clark et al (2000) evaluated an interactive seminar for GPs, and showed a short-term improvement in a subset of intervention group patients; these patients who had received an inhaled corticosteroid during the trial had fewer hospital admissions and scheduled visits for asthma but, after two years, only the reduction in hospital visits was sustained (Clark, Gong et al. 2000).

The second study identified in the review was an investigation into the effectiveness of an intensive small group education and peer review programme. The intervention aimed to educate GPs on the aims of the national guidelines on asthma/chronic obstructive pulmonary disease (COPD), including diagnosis, treatment, review and patient education (Smeele, Grol et al. 1999). The intervention consisted of four, two-hour intensive, interactive group education and peer review sessions. Patient outcomes included disease specific quality of life, current smoking and symptoms, but no significant changes compared to the control group were found for any of these outcomes.

The educational intervention in the third study involved seven small group seminars and group discussion focussing on asthma management strategies (White, Pharoah et al. 1989). Self-completed morbidity questionnaires were used to assess patient outcomes at six-monthly intervals over two years. There was no difference in morbidity between the groups before or after the intervention.

This review concluded that the three studies provided minimal evidence for the effectiveness of the different brief continuing medical education models used for improving health outcomes of patients with asthma treated in primary care (Barton, Sulaiman et al. 2003).

A cluster randomised controlled trial of educational interventions to improve detection rates for dementia in primary care compared three different approaches to the mode of delivery (Downs et al. 2006). An electronic tutorial on CD Rom which enabled learning from case analysis, a decision support software incorporated into the existing medical record software used in primary care, which gave prompts for the investigation and management of dementia, and small group workshops with GPs and practice nurses led by experienced GPs with a background in postgraduate education, were compared with a control group. Outcomes for this study were detection rates and concordance with guidelines; there were no patient-level outcomes. There were significant improvements in rates of reported cases of dementia with decision support software and practice-based workshops compared with the control group, however there was no difference in concordance with guidelines. This improvement may however have resulted from baseline differences,

Decision support software is considered to be a simple and practical intervention to implement in primary care. This study was included in a systematic review of the effects of educational interventions on primary care dementia (Perry et al. 2011), which showed moderately positive effects of educational interventions on dementia detection and diagnosis in primary care. Similar studies of educational interventions for suicide prevention (Morriss et al. 2005) and management of breast/ovarian cancer cases (Watson et al. 2001) conclude that brief interventions show only moderate effects which in some cases are not sustained.

More multifaceted interventions based on assessment of potential barriers to change have been reported to be the most effective (Grimshaw, Shirran et al. 2001). A cluster trial of a package of training for health visitors to identify symptoms of depression post-natally and to provide one-to-one sessions with participants was clinically effective in reducing depressive symptoms (Morrell et al. 2009), however Puder et al (2011) undertook a multifaceted lifestyle intervention to improve aerobic fitness and reduce body mass index (BMI) in preschool children (Puder et al. 2011), and used workshops, lessons, home activities, extracurricular activities and medications in the environment. Despite this intense level of intervention there was no change in BMI in preschool children, one of the primary outcome measures. Combinations of complex organisational and educational interventions for physicians and patients, together with enhanced involvement of health care professionals have been shown to improve depression outcomes in primary care (Gilbody et al. 2003). Similar complex multifaceted primary care trials reported no difference in primary outcome measures (Moore et al. 2003; Khunti et al. 2012).

Educational interventions for health professionals are important for improving the quality of health care (Wensing 2008), however there is a large variation in their effectiveness and it is difficult to predict from the evidence in the literature whether any intervention will lead to improved patient outcomes. When planning the trial presented in this thesis, this variable evidence was outweighed by the fact that short courses are routinely used as an educational tool by the NHS, and if this cheap educational intervention may have the potential to (Clark, Gong et al. 2000; Downs, Turner et al. 2006) impact patient outcomes, evidenced by a well-powered cluster randomised trial, there was benefit in testing it.

1.12. Systematic review of educational interventions in primary care targeting adolescent hay fever.

1.12.1. Introduction

Any intervention should be evidence based and rigorously evaluated prior to implementation in routine care. The need for an intervention to improve outcomes for adolescents with hay fever is clear, the prevalence is high in this population (International Study of Asthma and Allergies in Childhood 1998), and loss of productivity, poor academic achievement and loss of quality of life are well documented (Vuurman, van Veggel et al. 1993; Juniper, Guyatt et al. 1994; Kremer, den Hartog et al. 2002; Blaiss and Group 2004; Walker et al. 2007). Sheikh et al 2007 (Sheikh et al. 2007) showed that an educational intervention in primary care targeted at adults with perennial rhinitis had a moderate effect on patient outcomes.

This systematic review aimed to find any similar trial targeting adolescents with hay fever.

1.12.2. Methods

Criteria for considering studies for this review

Types of studies

This review was limited to randomised controlled trials.

Types of participants

All patients aged 12-18 years (adolescents) with a current seasonal allergic rhinitis diagnosis were included.

Types of interventions

Any educational intervention was included.

Types of outcomes

Outcomes were limited to quality of life for seasonal allergic rhinitis

Search methods for identification of studies

Literature was searched from 1946 to April 2014. Medline, Embase and the Cochrane Central Register of Controlled Trials were searched; there were no language restrictions applied.

The search strategy for Medline and Embase was:

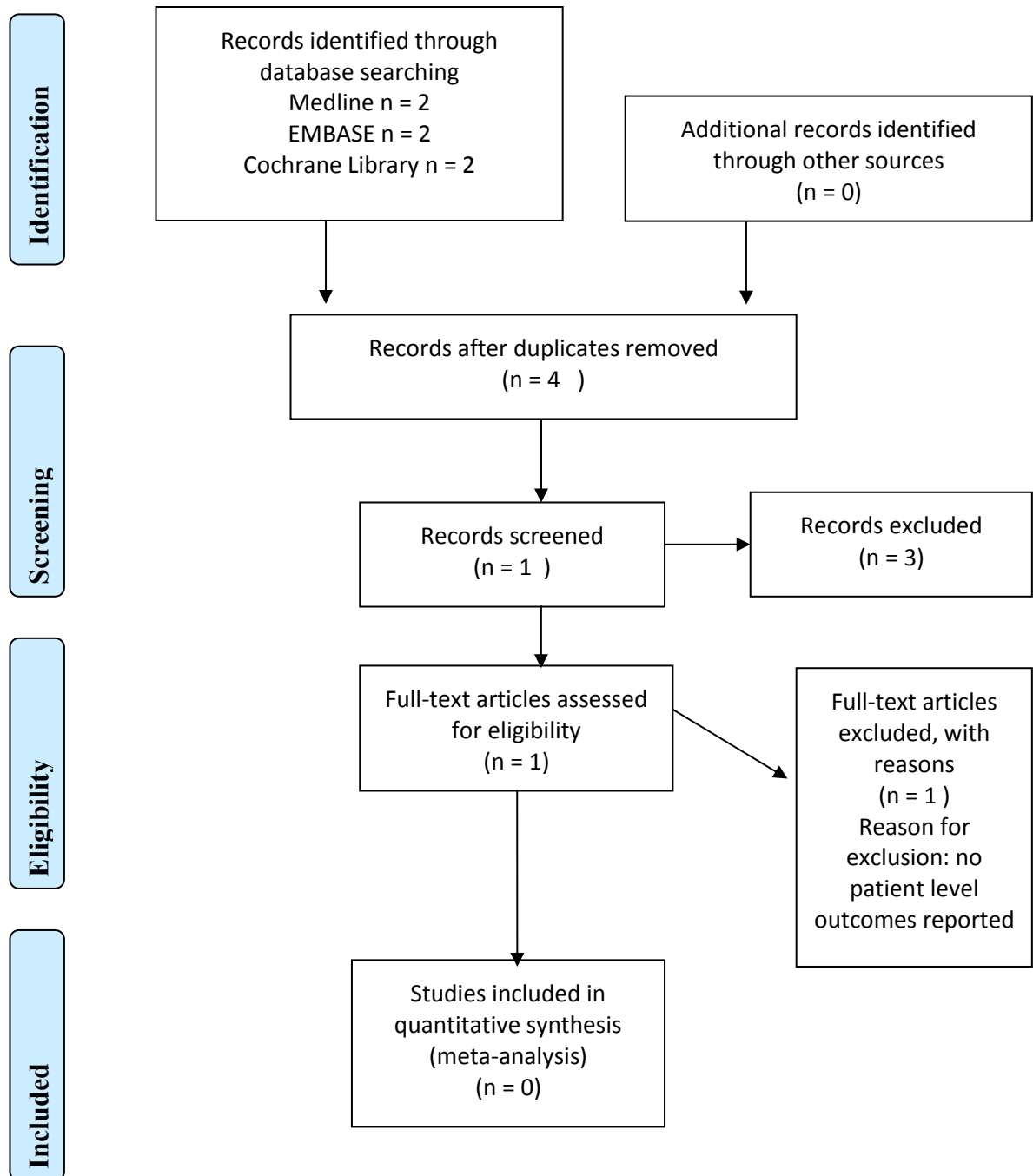
1. Rhinitis, Allergic, Seasonal/
2. Adolescent/
3. educational intervention.mp.
4. Primary Health Care/
5. 1 and 2 and 3 and 4

The search strategy for Cochrane Library was:
seasonal allergic rhinitis and educational interventions.

1.12.3. Results

There were no eligible studies. The searches revealed two conference abstracts relating to the current trial (Hammersley et al. 2010; Hammersley et al. 2010), the current trial protocol (Hammersley et al. 2010) and one further study (Mendez et al. 2008) (see Figure 1.1). After screening of the one study not related the current trial this was excluded as although it was an educational intervention targeted at primary health care professionals, there were no patient level outcomes reported.

Figure 1.1 Study Flowchart (PRISMA template)



1.12.4. Discussion

The search criteria for this systematic review were very specific; evaluations of educational interventions targeting primary health care professionals, reporting outcomes at the patient level and therefore it is not surprising that there were no relevant studies found. This finding therefore provided a clear rationale for the planned evaluation of an educational intervention in a primary care setting.

1.13. Context of the project development and rationale for the trial

The trial described in the thesis developed as a result of a successful Chief Scientist's Office (CSO) Research Training Fellowship application. In planning my CSO application I discussed research ideas with the senior academic staff in the Centre for Population Health Sciences. Professor Sheikh and Dr Walker (from Education for Health) had recently published a randomised controlled trial of an educational intervention for perennial rhinitis in adults (Sheikh, Khan-Wasti et al. 2007) and were interested in extending this work to explore a similar educational intervention for seasonal allergic rhinitis in adolescents. The requirements for the CSO Fellowship were to independently undertake a research project and complete a programme of research training. In collaboration with Professor Sheikh and Dr Walker I developed a proposal for a randomised controlled trial, and to register for a PhD as my research training. During the interview for my CSO Fellowship, we discussed the merits of a cluster randomised controlled trial methodology for evaluating educational interventions, and it was agreed that this trial would add valuable evidence if this approach was used, rather than a parallel group design; however it was also acknowledged that recruitment into cluster trials can be more

difficult and this part of the trial may be challenging. I was awarded a part-time research training fellowship for three years and registered for a part-time PhD.

The clinical basis for a trial of an educational intervention for hay fever in all age groups is clear, as despite the availability of cost-effective medicines and the grade A evidence of their efficacy (Sheikh, Panesar et al. 2009), morbidity from allergic rhinitis remains high (International Study of Asthma and Allergies in Childhood 1998) resulting in unnecessary symptoms, leading to time off school/work and therefore loss of productivity and a reduction in QoL for allergic rhinitis sufferers (Juniper, Guyatt et al. 1994).

Evidence that hay fever is a particular problem for adolescents comes was presented in a case-control study (Walker, Khan-Wasti et al. 2007) which investigated whether seasonal allergic rhinitis adversely impacts examination performance in UK teenagers. This was the first study looking at the effect of hay fever on examination performance, which is pertinent due to the General Certificate of Secondary Education (GCSE) examinations and peak grass pollen counts occurring simultaneously from mid-May to the end of June. Walker et al (Walker, Khan-Wasti et al. 2007) focussed on examinations in three core subjects taken by all students, namely Mathematics, English and Science (Walker, Khan-Wasti et al. 2007). Young people with seasonal allergic rhinitis symptoms were 40% more likely to drop a grade between their practice and final GCSE examinations (odds ratio: 1.43; 95% CI 1.13-1.18), and 70% more likely to drop a grade if they reported taking sedating antihistamines at the time of their examinations (odds ratio: 1.71; 95% CI 1.06-2.75).

The achievement of optimal outcomes in young people with hay fever depends on timely diagnosis, followed by implementation of measures to reduce allergen exposure, selection of safe and effective treatments and patient adherence to therapeutic regimens. This could possibly be facilitated by appropriately trained health care professionals who in turn can educate patients in the optimum treatment choices, which aim to: minimise or eliminate symptoms, optimise QoL and reduce the risk of developing co-morbidities, optimise timing of medication commencement, and improve techniques to ensure appropriate delivery of intranasal treatments.

A multi-centre community based RCT trial showed that standardised allergy education given to health care professionals improves disease-specific quality of life in adult patients with perennial rhinitis (Sheikh, Khan-Wasti et al. 2007). This collaborative study was carried out by The University of Edinburgh and Education for Health and found that a structured educational intervention was feasible to deliver in primary care and improved outcomes in adults with perennial rhinitis. This educational intervention was a six month diploma, distance learning allergy course supported by study days and examinations. This approach to continuing professional development requires considerable investment in time and resources, and given that much of healthcare professional's training is delivered in short course format, Education for Health developed an intensive short course focussing specifically on allergic rhinitis and asthma which was derived from one module of the diploma course. This short course was well attended and received by health care professionals, indicated by internal course evaluation (data not available), but had not been evaluated formally in terms of improved patient outcomes. Building on these

earlier studies (Sheikh, Khan-Wasti et al. 2007; Walker, Khan-Wasti et al. 2007) and the suggestion that short courses were more convenient and acceptable to busy primary healthcare professionals, this trial sought to evaluate whether Education for Health's intensive short course could improve outcomes for adolescents with hay fever.

1.14. Aims of the trial

The aims of this trial were therefore to:

- Establish the effectiveness of standardised allergy training for primary health care professionals in increasing disease-specific QoL of adolescents with hay fever
- Assess whether primary care-based health care professionals attending a hay fever focused intensive short course can enhance their self-assessed competence and confidence in managing adolescents with hay fever
- Measure any differences in clinical practice, consultations and/or prescribing between the control and intervention arms
- Assess any reduction in adolescent hay fever symptoms

Summary

This chapter presented the background information considered in the development of the trial. Consideration was given to the prevalence of hay fever and other allergic disorders, what current primary care treatment options are recommended in line with evidence-based guidelines current at the time of the intervention used in the trial, how hay fever affects the QoL of sufferers and how interventions may help this. The findings of the literature review of educational interventions in primary care were

unclear as to their benefits in terms of patient outcomes, however the results of the systematic review provided a clear rationale for proceeding with the cluster trial. The next chapter discusses the rationale for deciding to undertake a cluster RCT design and the methodological considerations of designing and running such a trial in primary care.

Chapter 2 – Methodology

Having outlined the background to the trial, this chapter will involve a review of existing guidance for carrying out a cluster RCT of an intensive short course in primary care, and in particular the specific methodological considerations of cluster randomised trials, which informed the decisions made in the trial design.

2.1. Introduction

When planning and designing a research study it is important to consider all possible approaches and methods that best address the research aims proposed. The theoretical framework which underpins a quantitative approach aligns itself with a positivist paradigm: that a single reality exists that can be measured (Kuper et al. 2008). Quantitative research is a formal objective deductive approach in which cause and effect can be explored, whilst the researcher strives to remain independent to the evaluation being undertaken (Malterud 2001). This is in direct contrast to a qualitative or naturalistic approach, where the researcher becomes an active participant in the research with the aim of developing a rich understanding of what people are actually experiencing and indeed identifying new research questions from this (Malterud 2001). Rather than believing that one reality exists, qualitative theory holds that the reality perceived is constructed by social, historical and individual contexts (Kuper, Reeves et al. 2008). Qualitative research is thus a more informal, subjective inductive approach used to develop theory rather than test it, and is used to explore, for example, social experience, attitudes and meanings, processes relating to interactions, all of which are integral components of clinical knowledge. Acknowledging the strengths and limitations of both quantitative and qualitative paradigms has led some to consider, where appropriate, a mixed-methods approach,

where qualitative and quantitative methods are integrated within the same study (Cresswell et al. 2012). This assumes that the knowledge gained from each analysis is complementary and enriching.

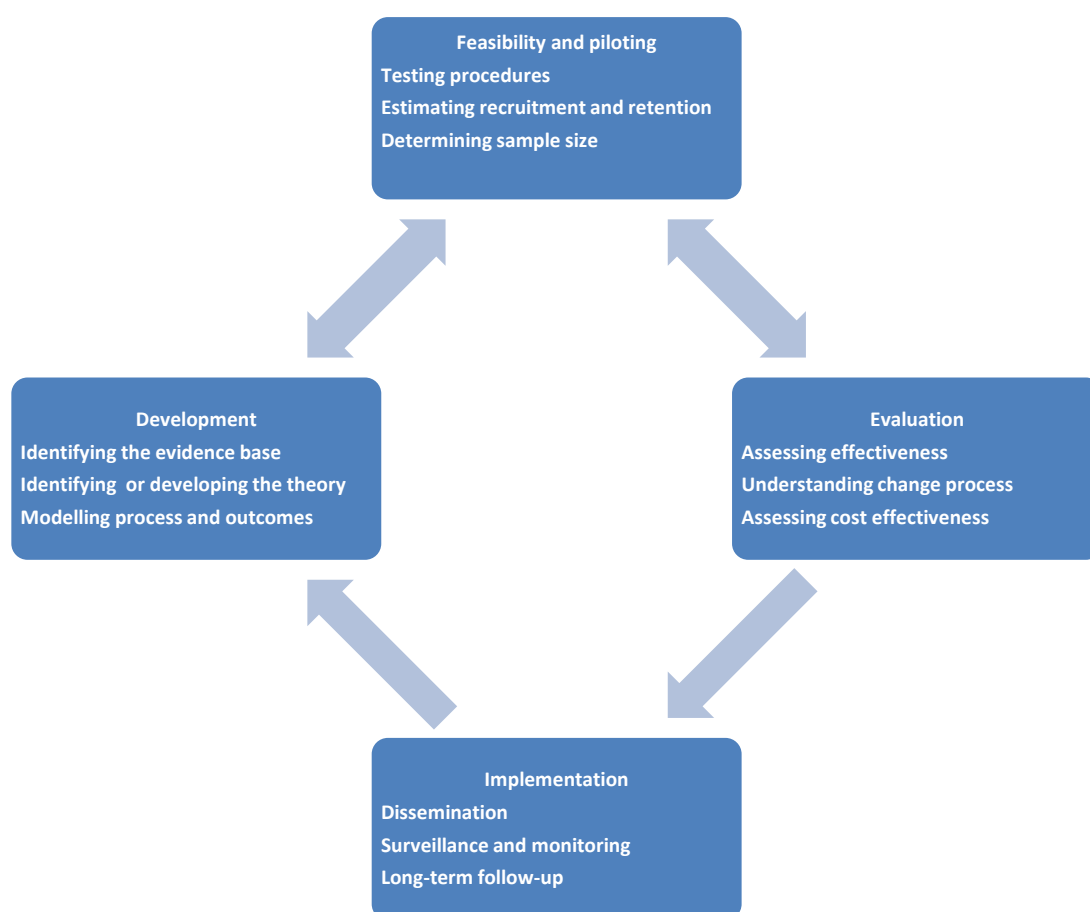
2.2. Complex interventions

Complex interventions are described as interventions that contain several interactive components (Medical Research Council 2000). One could argue that no intervention is simple, but the number of possible dimensions of complexity varies. The original Medical Research Council (MRC) guidance on developing and evaluating complex interventions (Medical Research Council 2000) proposed a framework (Figure 2.1) to help researchers develop appropriate methods and this has subsequently been revised and updated (Craig et al. 2008). The framework advocates a flexible phased approach similar to that used in developing and testing drugs, which are:

- Development: exploring relevant theory to ensure the best choice of intervention and hypothesis, which includes developing a theoretical understanding of the likely process of change and may involve generating new evidence, and modelling to identify the components of the intervention and the underlying mechanisms by which they will influence outcomes;
- Feasibility and piloting: testing components of a replicable intervention, assessing acceptability, compliance, delivery of the intervention, recruitment and retention and estimates of effect size, and as discussed in Section 2.1 a mixed methods approach is likely to be needed to understand many of these important factors;

- Evaluation: consideration of all study designs available which suit different questions, choosing appropriate outcome measures, measuring processes which will be key to understanding causal mechanisms and outcomes.
- Implementation: getting evidence into practice is a fundamental premise of all research and the evidence should be available in accessible formats and disseminated widely.

Figure 2.1: Key elements of the development and evaluation process (taken from Developing and evaluating complex interventions: the new Medical Research Council guidance (Craig, Dieppe et al. 2008))



2.3. Randomised controlled trials

RCTs represent the methodology of choice for assessing the effectiveness of a health care intervention because of the unique ability to control for known and unknown confounding factors (Sheikh et al. 2002). For studies where the natural unit of analysis is the patient, but the intervention is delivered to a unit such as a general practice, it is necessary to conduct a cluster RCT in order to minimise the risk of contamination (Campbell et al. 2012). Cluster randomised designs are often used for intervention studies in primary care, where naturally occurring units or clusters such as general practices exist (Raab et al. 2001). Examples of this in primary care include a trial of obesity management (Moore, Summerbell et al. 2003), practice nurse training in the use of asthma action plans (Cleland et al. 2007), pharmacist led statin outreach support (Lowrie et al. 2010) and a pharmacist intervention to reduce medication errors in primary care (Avery et al. 2012).

2.4. Justification for a cluster RCT

There are a number of reasons to randomise at the cluster rather than at the individual level:

- The intervention occurs at a cluster level such as health care interventions in practices, hospitals or communities.
- To eliminate contamination of the intervention effects between patients in the cluster
- Patients in one cluster are likely to have similar outcomes.

Ukoumunne et al (1999) identified the following methodological problems with cluster trials (Ukoumunne et al. 1999):

- The level of the intervention may differ from the level of the evaluation
- There may be a small number of clusters
- Outcomes of individuals are often correlated within clusters.

Once randomising by cluster has been decided, these problems must be accounted for in the design, analysis and reporting of the trial, as lack of independence between patients in a cluster RCT has important statistical implications for sample size calculations and analysis (Eldridge et al. 2012). The CONSORT (Consolidated Standards of Reporting Trials) statement (Moher et al. 2001; Schulz et al. 2010) on trial conduct and reporting has been extended to take into account the special features of cluster RCTs (Campbell et al. 2004; Campbell, Piaggio et al. 2012), such as the rationale for cluster design, and implications of the cluster effect in design and analysis. A cluster RCT was the most appropriate design for this trial of a complex educational intervention delivered to health care professionals in primary care to avoid contamination between groups, and to account for the two levels, (the general practice and the patient). The implications on design, conduct, analysis and interpretation (Campbell, Piaggio et al. 2012) are considered below.

2.5. Design

2.5.1. Random allocation and minimisation

An essential part of RCTs is the process of allocating units (in this study the unit of allocation was the general practice) to the intervention and control arms. This process is known as randomisation and is essential to minimise systematic bias during the selection stage of a trial (selection bias). Randomisation ensures that any differences that are found between the two groups following an intervention can only be due to the intervention effect or chance (Hahn et al. 2005).

Minimisation is a method of trial allocation useful in trials with a small number of clusters and aims to ensure that treatment arms are balanced in terms of predefined patient factors as well as patient numbers in each group (Scott et al. 2002). It was originally described by Taves (Taves 1974) and Pocock (Pocock et al. 1975) in the mid-1970s, but despite being recommended for use in clinical trials it is not widely adopted as a method for allocation to trial arms in clinical trials. It is a non-random method of treatment allocation and can be criticised, as assignment to treatment arms may be predicted (Scott, McPherson et al. 2002).

2.5.2. Sample size considerations

When planning a cluster RCT, the standard methods for calculating a sample size that allow a reasonable chance of detecting a pre-determined difference in outcomes are not sufficient. The design of a cluster RCT is not as efficient as a trial that has used individual randomisation where outcomes are independent if the evaluation is at the individual level. This lack of independence may increase the size of the standard errors, widen confidence intervals and increase p values compared with a study of the same size using randomisation at the individual level (Campbell et al. 2000). The loss of statistical power resulting from a cluster design can be compensated by a statistical measure known as the ‘intraclass correlation coefficient’ (ICC) and to achieve the same power as an individual level randomisation, standard sample sizes need to be inflated by a factor known as the ‘design effect’ or ‘variance inflation factor’ (Donner et al. 2000). The design effect is defined as the ratio of the total number of participants required using cluster randomisation to the number required

using simple randomisation to detect the same treatment effect (Kerry et al. 2001).

This is calculated using the equation:

$$1 + (n - 1) \rho$$

where n is the average cluster size and ρ is an estimate of the ICC (Campbell, Mollison et al. 2000). Estimates of the design effect are ideally based on previously reported trials, which are as similar as possible in terms of size of cluster, types of individuals the intervention is aimed at and outcome measures used. There is little published literature about the likely design effect in health care interventions and have fewer quality of life, and despite the CONSORT guidance (Campbell, Piaggio et al. 2012), few studies in primary care report the estimated effect size and its precision, and an ICC for each primary outcome.

2.6. Analysis

The unit of analysis in a cluster RCT can be either the cluster level or the individual participants provided the clustering effect is accounted for. It is widely accepted that individuals within the same cluster (e.g. general practice) may be more similar than individuals selected at random (Campbell, Mollison et al. 2000). This lack of independence or correlation leads to loss of statistical power compared with individual patient randomisation, which needs to be accounted for in the analysis. For this reason, the use of standard statistical techniques commonly used in RCTs of individuals are not appropriate for cluster RCTs (Mollison et al. 2000; Lancaster et al. 2010). Failure to adjust for the clustering effect will give misleading results. Multi-level analyses that take account of both individual and cluster-level effects are increasingly reported in primary care trials (Morrell, Slade et al. 2009; Butler et al. 2013).

2.6.1. Missing data

Poor compliance in clinical trials collecting quality of life data is well recognised (Fielding et al. 2008) as with most areas of research. Missing data are more likely to occur with quality of life data than with clinical data for example, because they are generally self-administered and follow-up questionnaires are often posted to participants numerous times throughout a study, rather than being collected face-to-face (Fielding et al. 2012). The most fundamental information to ascertain when attempting to deal with missing data is the reason for ‘missingness’, as this has implications for the risk of bias that is associated with the missing data. Data may be missing for a variety of reasons, which are widely reported in the literature (Sterne et al 2009). Three main mechanisms defined by Rubin (Rubin 1976) are:

- Missing completely at random (MCAR): i.e. there are no systematic differences between the missing and observed values.
- Missing at random (MAR): Any systematic difference between the missing values and the observed values can be explained by differences in observed data.
- Missing not at random (MNAR): Even after the observed data are taken into account, systematic differences remain between the missing and the observed values.

Approaches to dealing with missing data include simple imputation, where a single estimate value for the missing observation is obtained (Fielding, Fayers et al. 2008), or multiple imputation where several different plausible imputed datasets are created and combined to obtain results from each of them. Complete case analysis is criticised in the literature for not taking account of the potential bias, however if data

are missing completely at random, there may be justification for a complete case analysis (Sterne et al. 2009).

Chapter 3 – Methods

The study design used was a cluster RCT. The unit of randomisation was the general practice. The health care professional at each trial site provided enhanced care (intervention) or current care (control) to adolescents suffering from hay fever. The trial took place over two summers: 2009 and 2010, in general practices in Scotland and England.

A protocol of the methods used in this cluster RCT was published in advance of analysis (Hammersley, Elton et al. 2010). The trial was registered on the Current Controlled Trials register: ISRCTN95538067.

3.1. Research ethics and research & development approval

The study was initially approved by Lothian Research Ethics Committee 02 (Reference 08/S1102/37) (see Appendix 1 for approval letter). In year 1 of recruitment, a substantial amendment was accepted by the ethics committee to extend the recruitment period for an additional year and broaden the recruitment base as described in Section 3.3.1 below (see Appendix 1 for approval letter). R&D approval was obtained from NHS Lothian, NHS South of Tyne and Wear, NHS North of Tyne, NHS County Durham, NHS North Yorkshire and York and NHS Leeds (see Appendix 1 for approval letters). The clinical trial was conducted according to the Helsinki Declaration (World Medical Association Declaration of Helsinki) and Good Clinical Practice Guidelines (Medical Research Council 1998).

3.2. Setting

The trial took place across Edinburgh, Lothian and Borders, Durham and Tees Valley, Northumberland Tyne and Wear and Yorkshire.

3.3. Recruitment

3.3.1. Recruitment of general practices

In the first year of the trial, the Scottish Primary Care Research Network (SPCRN) was approached for their assistance with practice recruitment in Lothian and Borders. They were asked to recruit 25 practices. SPCRN wrote to their member general practices informing them of the study with an information flyer. Where practices expressed an interest in participating, an information sheet and consent form was sent to each practice with the offer of a face-to-face or telephone discussion at which the study was explained in more details. A member of the practice team (Lead GP or Practice Manager) then signed a consent form if the practice decided to participate. Practices were asked to nominate a health care professional who regularly saw patients with hay fever, but who had not received postgraduate allergy training in the previous 12 months, to take part in the trial. After three months of recruitment effort by SPCRN only eight practices had been recruited. Following discussion with GP colleagues in the Centre for Population Health Sciences and the Trial Management Group, a variety of alternative methods were used to increase the uptake of the trial in Lothian and Borders:

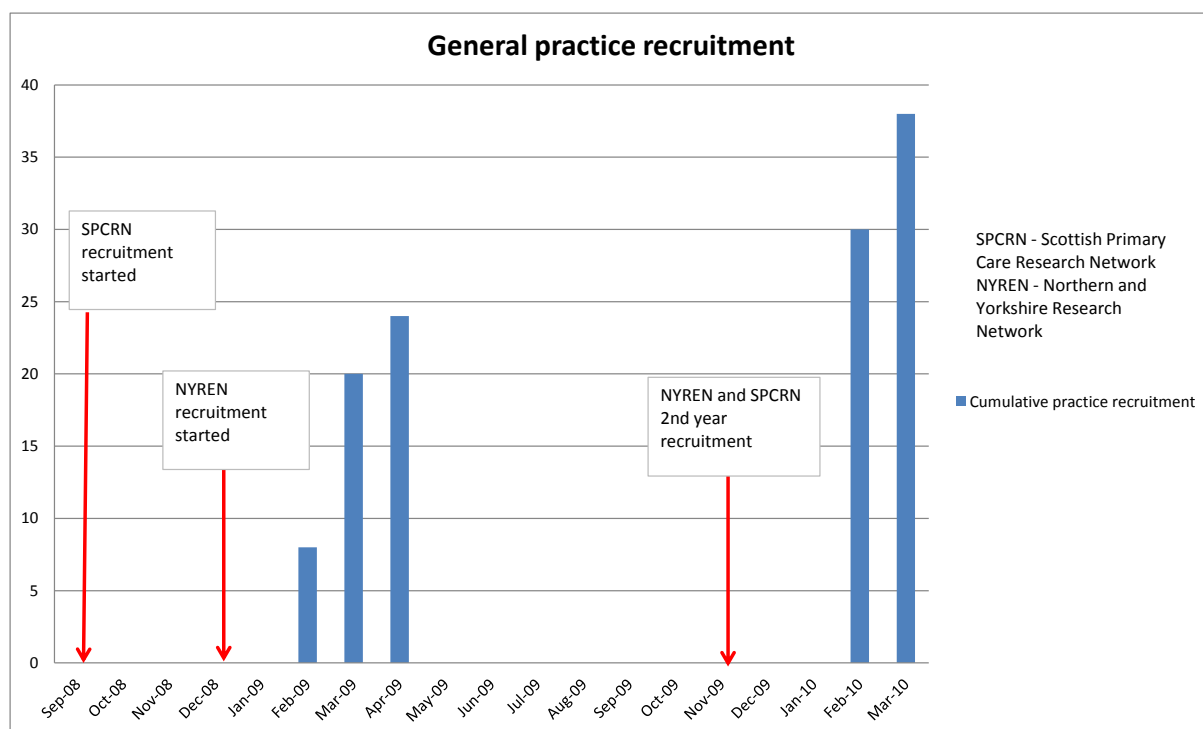
- Increased SPCRN mailing in Lothian and Borders followed by 2-3 telephone calls to practice managers/lead GPs
- Contact was made with general practices in Scotland via NHS Education for Scotland
- The Scottish Practice Nurse Association were contacted and agreed to mail information to their members and put a flyer on their website
- Education for Health mailed Scottish practice nurses on their training register

- Local Health Partnership practice nurse leads in Lothian agreed to advertise the trial at their meetings
- Local informal contacts were asked to discuss the trial with their practices

I delivered poster and oral presentations at seminars organised by the Centre for Population Health Sciences.

Despite this effort to increase the awareness of the trial in Lothian and Borders, we were unable to recruit any further practices. Following a discussion with a senior academic in CPHS who was working with English practices, I contacted the Northern and Yorkshire Research Network (NYREN), who have a different model for general practices to engage in research, which includes financial reimbursement. They have a membership of ‘research ready’ practices who are committed to take part in research annually, as well as practices who are aiming to become research ready. Following a successful application process to NYREN and all the additional ethics and R&D approvals being in place, 11 practices were recruited in just over three weeks via NYREN. Figure 3.1 shows recruitment of general practices over the two years, demonstrating the slow recruitment rate in the first year compared with the second year.

Figure 3.1: Cumulative practice recruitment over two years from two primary care research networks.



3.3.2. Recruitment of adolescents

Patients with a recorded diagnosis of hay fever (Read code clinical terms v2: H17), and/or evidence of use of hay fever medication in the previous two years (oral antihistamines and topical steroids, drugs used in nasal allergy and topical nasal decongestants; Read code clinical terms v2: c8, c6, 18 and 19) were identified via the general practice medical records using a standardised search (Hammersley, Flint et al. 2011). Patients who were identified as having a relevant hay fever medication then had their medical records checked to ensure that the medication was for hay fever rather than another allergic disorder, to exclude any false positives where possible. As required by the ethics committee, a member of the practice team also screened the list of patients identified for suitability to take part in the trial. Staff

were asked to be as inclusive as possible and to state a reason for exclusion (see Appendix 2).

The practices were then asked to write to eligible participants sending an invitation letter (see Appendix 3) with a participant information sheet, consent form and patient data collection form (see Appendix 4, 5 and 6) and a reply paid envelope for return directly to the study team. These letters were signed by either a GP or practice nurse and printed on practice letter headed paper. An Excel spreadsheet of eligible patients was created and stored on a practice computer, and this was used to identify patients who did not respond and therefore needed a reminder. Reminder packs were sent to non-responders by the practice nurse two weeks after the initial mailing.

During the planning of the trial consideration was given as to how to engage the adolescent participants and maximise compliance with the protocol. The key time points for reminders for participants were two weeks following the mailing of the questionnaires and the night before the health care professional consultation. Previous work has shown that mobile phone short messaging service (SMS) can be used effectively in research involving adolescents and that it is feasible and useful as a reminder tool (Gurol-Urganci et al. 2013; Balzer et al. 2014). Consenting patients were asked to express their preferred method of communication with the research team: email, mobile phone short messaging service (SMS) or post and the method of communication with each participant was individually tailored to their choice.

3.3.3. Inclusion criteria

General practices:

- General practices that were within the recruitment areas of the SPCRN and NYREN that agreed to participate in the study
- General practices that were willing to allow a nominated health care professional to attend a one-day training workshop on allergic rhinitis and asthma

Patients:

- All young people aged 12-18 years with a clinical diagnosis of hay fever defined by the presence of a documented clinician diagnosis in their health record and/or any evidence of treatment used for hay fever
- Patients who returned a signed consent form.

3.3.4. Exclusion criteria

General practices:

- General practices not interested in participating
- General practices unable to release practice staff to attend the training.

Patients:

- Patients who were found to be false positives for hay fever on closer examination of their medical record
- Patients who were screened out by appropriate medical staff
- Patients who did not return the consent form.

3.4. Randomisation and minimisation

Randomisation to intervention or control was carried out separately within each of the five participating regions: Lothian; Borders; Durham and Tees Valley;

Northumberland Tyne and Wear and Yorkshire. For the four regions with more than two practices, this was done using a centralised minimization scheme according to the methods described by Carter and Hood (Carter et al. 2008) in order to achieve an optimum balance for practice list size and deprivation scores (see Appendix 7). The randomisation was carried out by a statistician who was independent of the recruitment of clusters and patients.

The reason for randomisation by centre was to help ensure an even distribution of intervention and control practices as there was likely to be a geographical variation in pollen counts between centres. In order to minimise selection bias, practices were not randomised until all patients had been identified from electronic searches and invited by mail to participate.

3.5. Sample size

Using data from a parallel group study which used the RQLQ in adults with perennial rhinitis (Sheikh, Khan-Wasti et al. 2007), a mixed-model analysis of variance (Murray 1998) was calculated in SPSS and gave an F-ratio of less than unity, indicating that there was less variation between practices than would be expected by chance. This means that the inter-practice variance and hence the ICC was estimated as zero, and there would thus be no anticipated DE for the proposed cluster RCT. There are obvious differences between the study in adults and this cluster trial in adolescents, including the trial design. An ICC of 0.02 was therefore chosen based on a range of ICCs reported in previous work in primary care (Ukoumunne, Gulliford et al. 1999; Moore, Summerbell et al. 2003).

In order to determine the potential cluster size for the trial, two general practice databases were searched using a standard search strategy (Hammersley, Flint et al. 2011). This search suggested that between 19 and 36 patients would be eligible based on these two practices with relatively small list sizes (5196, 6376 respectively). A cluster size of 10 was chosen based on these numbers, in the hope that it would be possible to recruit at least this number of adolescents with diagnosed current hay fever from most general practices.

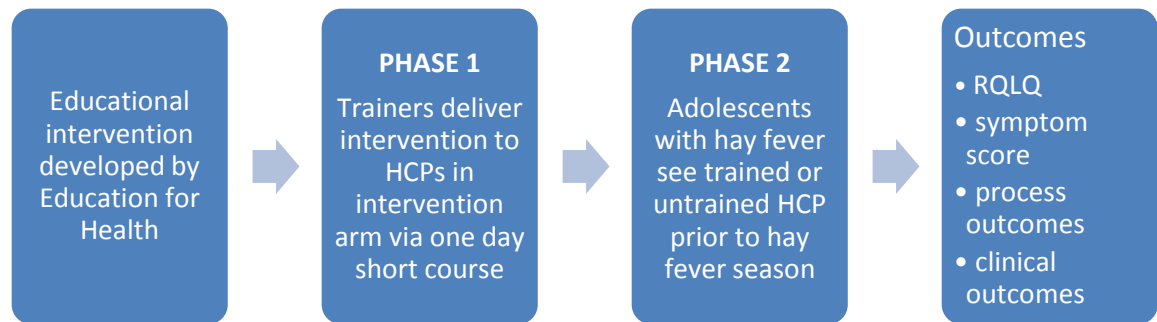
Taking account of the cluster design, using a standard deviation of 1.2 (Juniper, Thompson et al. 2002) with a power of 80% to detect a minimal clinically important difference of 0.5 (Juniper, Guyatt et al. 1994) in RQLQ(S) score at a significance level of 5%, an estimate of the cluster size of 10 and an ICC of 0.02 required a total of 22 clusters and an adjusted sample size of 220 patients (unadjusted 180). Sampsize was used for sample size calculations (Campbell et al. 2004).

Based on these figures, at least 22 general practices were required to recruit 10 patients each. Assuming that there would be some loss to follow-up, this patient number was inflated by 20% resulting in 22 clusters recruiting 12 patients per practice, giving a total of 264 patients in the study (i.e. 132 per arm). With these numbers, the study was sufficiently powered (80%) for the primary outcome measure.

3.6. Intervention arm

The intervention was in two phases: the first phase was at the level of the practice/health care professional and the second at the level of the patient.

Figure 3.2: Pictorial representation of the process for this intervention



(HCP –Health care professional)

3.6.1. Educational intervention

Nominated health care professionals allocated to the intervention arm were invited to attend a one day intensive short course ‘Essentials of Allergic Rhinitis’ (and its impact on Asthma) run by Education for Health, a charity which focuses on the education of health professionals with the aim of improving patient health and quality of life. In seeking to mirror the ways in which the majority of UK health care professionals receive their continuing professional education, an intensive, evidence-based one day course was developed by Education for Health from a diploma level allergy course. This course provided a basic understanding of allergic rhinitis and related conditions including asthma, and aimed to equip health care professionals with the knowledge, skills and expertise to support adolescents to optimally manage their hay fever. For the purposes of the trial, the short course was adapted to increase its salience to the management of hay fever in adolescents. This adaptation was undertaken by Education for Health’s course development staff in conjunction with the two trainers who delivered the course.

The interactive course began with an assessment of the participant's current allergy knowledge, followed by the presentation of a case study of a child with a history of infantile atopic eczema/dermatitis, from a smoking family, history of parental asthma and who have three pets. The delegates were asked to consider the question:

'What would make you suspect a diagnosis of allergic airways disease in this child?', which led on to a discussion about the importance of getting the diagnosis of allergy correct, focussing on history taking including family history and treatments prescribed as well as the impact any symptoms could be having on the child's QoL. This case study was referred to throughout the whole training day to reinforce key learning points and consider the progress of allergic disease throughout childhood and adolescence.

The second session gave a brief overview of the pathophysiology of allergy including classification of allergy, before moving into a more detailed discussion of this in the context of hay fever. Making a diagnosis from history taking and examination was followed by a description of methods used to confirm a diagnosis, such as SPT for common aeroallergens such as mixed grass and tree pollen, and tests for specific IgE. Delegates were then given a very brief overview of food allergy and atopic eczema/dermatitis.

Session 3 of the day focussed on the management of allergic airways, and considered allergic rhinitis as a risk factor for asthma as well as a disease causing considerable morbidity in its own right. Evidence from a case-control study on the impact of hay fever on examination performance (Walker, Khan-Wasti et al. 2007) was presented and discussed. Delegates were given a copy of the British Society for Allergy and

Clinical Immunology (BSACI) allergic rhinitis algorithm (Scadding, Durham et al. 2008), and all treatment discussions were based on ARIA (Bousquet, Khaltaev et al. 2008) and the British Guideline on the Management of Asthma (British Thoracic Society/Scottish Intercollegiate Guidelines Network 2008) for the management of allergic rhinitis and asthma respectively which were current at the time of the study. It was felt by the trainers and the research team that it would be important for the health care professionals to have a good understanding of management of asthma as well as allergic rhinitis for two reasons: firstly the total steroid dose for hay fever sufferers with comorbid asthma was discussed for patients who may be prescribed a nasal steroid, and secondly, it was suggested that including strategies for managing patient's hay fever in a patients annual asthma review may be opportunistic, but beneficial in terms of treatment for both diseases.

Embedded within the short course were practical sessions on nasal spray and inhaler device technique. There was ample time for individual and group discussions to ensure that individual learning styles were met and any queries were addressed. The final session asked delegates to consider the question: *‘What are you going to do when you return to your practice?’*

Delegates were prompted to think about how they might raise awareness of the impact of poorly treated hay fever in their patients, particularly adolescents; whether changes could be made to improve Read coding to ensure patients with disease can be accurately identified; to consider what advice they would give to patients with

allergic disease and how they might put into practice tomorrow what they have learned today.

The course was delivered twice in the spring of each trial year prior to the hay fever season by Education for Health trainers.

3.6.2. Patient appointments with health care professionals

Practices were asked to allocate clinic times for the nominated health care professionals to see patients. Patients were informed to contact their practice to book an appointment convenient to them. Appointments were between 10 and 15 minutes, depending on the practice policy. Contact was made with the practice to ensure that all consenting patients had made an appointment during May-June 2009 and May-June 2010.

No guidance was given to either arm about the format of the consultation; however some health care professionals in the control arm did request help. All patients were reminded via their chosen method of communication 24 hours prior to clinic appointment.

3.7. Control arm

Health care professionals in the control arm were provided with a copy of the BSACI guidelines for the management of allergic and non-allergic rhinitis (Scadding, Durham et al. 2008) (see Appendix 8).

3.8. Outcome measures

3.8.1. Primary outcome

The primary outcome was:

- The changes in RQLQ(S) score between baseline and 6-8 weeks post-intervention in the control and intervention arms (see Appendix 9 for RQLQ(S)).

3.8.2. Secondary outcomes

The secondary outcomes were:

- Patient reported symptom scores using a visual analogue scale

Patients were asked to indicate their overall hay fever symptoms as a visual analogue score (scale 0-10) in response to the question: ‘How has your hay fever been this week?’ (see Appendix 10 for visual analogue scale).

- Number of consultations for hay fever, number of prescribed medication

The total number of consultations with reasons and prescriptions between the date the patient was seen for the trial and the end of August 2009/10 were extracted from their medical records.

- Assessment of change in clinical practice in the intervention arm

Health care professionals in the intervention arm completed a questionnaire at three time points: immediately prior to the training intervention, immediately post-training intervention and, after they had seen all the patients in the trial. This questionnaire measured the effects of the training on skills and confidence following the training using a Likert scale where a score of 1 = less confident/likely and 5 = more confident/likely.

3.9. Data collection

3.9.1. Cluster characteristics

Baseline data collection for clusters included deprivation scores (SIMD and IMD 2004) which were obtained from the Information Services Division (ISD) of NHS National Services Scotland (<http://www.isdscotland.org/>) for the Scottish clusters and the Office of the Deputy Prime Minister website (www.odpm.gov.uk) for the English clusters. List size was obtained from ISD for Scottish clusters and from the practice managers for the English clusters.

3.9.2. Baseline patient data

Consenting patients were asked to complete a baseline data collection form which included basic demographics such as date of birth and sex as well as information about the duration of their hay fever and current medication. Primary and secondary patient reported outcomes were measured at the beginning of the hay fever season prior to the clinic appointment. Patients were reminded to complete their baseline RQLQ(S) and symptom score by email, SMS or telephone call to ensure they were returned prior to their clinic appointment. Practice nurses were requested to check that every patient had completed the baseline questionnaires at the beginning of the appointment. To maximise completion rates, if the patient had not completed the baseline questionnaire, copies were given to the patient for self-completion before the consultation started.

3.9.3. Process data

Consultation and prescribing data were collected from the general practices for all patients from the date of consultation for the study to the 31st August 2009 or 2010.

For each patient, every consultation with reason and every prescription within the above timeframe was recorded. Numbers were totalled for the following categories:

- number of consultations
- number of consultations for hay fever
- number of consultations for other respiratory conditions
- number of prescriptions
- number of prescriptions for hay fever

3.9.4. Follow-up 6-8 week questionnaires

RQLQ(S) and a visual analogue scale for recording symptoms scores along with reply-paid envelopes were sent to each patient within 6 weeks of their health care professional consultation, which covered a period of predicted peak pollen counts based on pollen data from previous years. Reminders to complete and return the questionnaires were sent by SMS, post or email. A second set of questionnaires with reply envelopes were sent to non-responders two weeks after the initial mailing.

3.9.5. Pollen data

In order to assess whether the pollen count reached a level which may induce hay fever symptoms during the study period, and when that potential peak happened in relation to the patient data collection for primary and secondary outcomes, pollen data were collected. Grass pollen data were available for the 2009 and 2010 seasons in two sites: Edinburgh and York. Data from Newcastle were not available for these two years, however data were provided for 2007 and 2008. The pollen count is a measure of the number of pollen grains of a certain type per cubic metre (pgm^3) of air sampled, averaged over 24 hours. The pollen forecast is usually given as low ($<30 \text{ pgm}^3$), moderate ($30\text{-}49 \text{ pgm}^3$), high ($50\text{-}149 \text{ pgm}^3$) or very high (\geq

150 pgm^3). Most sufferers will start to experience symptoms when the count reaches the moderate category. Data were obtained from NPARU at the University of Worcester, as well as directly from researchers based in Edinburgh and York.

3.10. Missing data

The RQLQ(S) is divided into seven domains with varying numbers of questions per domain. The overall RQLQ(S) score is calculated from the mean of each domain. Where responses to a whole domain were missing, the patient was excluded from the analysis.

An intention-to-treat analysis was proposed on all those with only baseline RQLQ(S) using the last observation carried forward, but this was not appropriate as imputing of the baseline data (which was collected before the pollen season) for subjects whose final RQLQ(S) were missing would not be conservative, since the lack of change from a value measured before the hay fever season might be better than expected (i.e. baseline values may be low on a scale of 0-6, where 0 is not troubled and 6 is extremely troubled). Imputing this data for an RQLQ(S) measured at the peak of the season, which may have been high, might result in over-estimation of the intervention effect if more cases had missing data in the intervention arm. A complete case analysis provided unbiased estimates under the assumption that the missing data are 'Missing Completely at Random' (Rubin 1976), however a preliminary analysis of the means estimated for each pattern of missingness suggested that this assumption may not hold. Further sensitivity analysis based on the following assumptions was therefore carried out:

- The direct likelihood method (Molenberghs et al. 2007): The primary analysis of the effect of the intervention on RQLQ(S) was repeated, but with the baseline score modelled jointly with the outcome at six weeks instead of entering the model through the linear predictor. Using this model allowed for the inclusion of all 309 patients with data on at least one occasion and provided likelihood estimates that are valid under the MAR assumption (Rubin 1976).
- Multiple Imputation: Proc MI in SAS was used to generate multiple imputations (m=100 imputations) separately for each treatment arm (pooling across centres).
- Alternative sensitivity analysis under MNAR: Sensitivity analyses under a MNAR assumption were carried out based on two assumptions: 1. that missing values in any particular cluster (at baseline or follow-up) were equal to the largest observed score from that cluster (and time point) (poor outcome), and 2. that missing values in any particular cluster (at baseline or follow-up) were equal to the lowest observed scores from each cluster (and time point) (good outcome) to impute missing values.

3.11. Data analysis

All data were double entered by two independent people, and checked for errors using SPSS (version 14, 2005). Discrepancies identified were checked from the original source and amended, and the data were checked again until no discrepancies were identified.

3.11.1. Cluster characteristics

Data were compared for list size and deprivation scores between participating (n=38) and non-participating practices (n=204), and intervention (n=20) and control practices (n=18) using two sample t-tests in SPSS (version 14, 2005).

3.11.2. Patient characteristics

Patients in the intervention and control arms were compared for age and sex.

3.11.3. Primary outcome

Complete case analysis was undertaken. In the analysis of RQLQ(S), multi-level modelling using a random effects model (MLWin (version 2.20, 2010)) was used to take account of between and within cluster variation, adjusting for baseline score, strata, individual covariates and year of study. Estimates and confidence intervals of the intervention effects were calculated for the RQLQ(S). Patterns of missing data at the two data collection time points and between the intervention and control arms were explored.

3.11.4. Secondary outcomes

In the analysis of symptom score, multi-level modelling using a random effects model was used to take account of between and within cluster variation, adjusting for baseline score, strata, individual covariates and year of study. Estimates and confidence intervals of the intervention effects were calculated for the symptom score.

Differences between the two arms for the process measures of number of consultations and prescribing data were analysed using multilevel analysis in

MLWin (version 2.20, 2010). Differences in the mean scores of self-reported knowledge and confidence in the intervention arm were compared using t statistics.

3.11.5. Estimates of the ICC

Two alternative approaches were taken to estimate the ICC using RQLQ(S) data from the adult perennial allergic rhinitis trial referred to previously (Sheikh, Khan-Wasti et al. 2007) and this trial of adolescents with hay fever: a mixed-model analysis of variance using SPSS (version 14, 2005), and a Bayesian approach (which acknowledges that an ICC cannot be negative) using WinBUGS (1.4 2009) using a uniform prior of 0-1 (uniform on ICC) (Spiegelhalter 2001).

Chapter 4 – Results

This chapter presents the results of the cluster RCT. Baseline characteristics of the general practices (clusters) and the target population of adolescents with a diagnosis of hay fever are presented with the flow of clusters and participants through the trial following the CONSORT guidelines for cluster trials (Campbell, Piaggio et al. 2012).

4.1. Baseline characteristics

4.1.1. General practices (clusters)

Thirty eight general practices (clusters) agreed to participate in the study, 20 were randomised to the intervention arm and 18 to the control arm. Clusters were comparable for baseline characteristics in terms of deprivation; however the intervention practices had a larger mean list size (see Table 4.1). No differences were found in terms of list size and deprivation between the participating and non-participating practices (see Table 4.2).

Table 4.1: Baseline information for each arm at individual and cluster level

	Intervention Arm	Control Arm
Practice factors		
Number of clusters	20	18
Mean list size	11144	8330
Mean deprivation score		
IMD ¹	21.5	21.7
SIMD ²	2.48	2.47
Participant factors		
Number	223	118
Mean age (years) (sd)	15 (1.85)	15 (1.91)
Number (%) male	112 (50.2)	57 (48.3)

¹IMD - The 2004 Index of Multiple Deprivation for English practices

²SIMD - Scottish Index of Multiple Deprivation

Table 4.2: Comparison of demographics of participating and non-participating practices in England and Scotland

	Participating practices (n=38) Mean (SD)	Non-participating practices (n=204) Mean (SD)	P values
Scottish sites (n=7)			
List size	6562 (3363)	6971 (3302)	P=0.75
SIMD ¹	2.69 (0.67)	2.60 (0.70)	P=0.76
English sites (n=31)			
List size	8707 (4048)	7464 (4847)	P=0.19
IMD ²	26.8 (18.2)	31.0 (19.6)	P=0.27

¹SIMD - Scottish Index of Multiple Deprivation

²IMD - The 2004 Index of Multiple Deprivation for English practices

4.1.2. Participants

Of the patients assessed for eligibility from the general practice medical records, 1565 satisfied our inclusion criteria and of these 341 (22%) agreed to participate (Figure 4.1). Participants were comparable at baseline in terms of age and sex profile.

More patients were randomised to the intervention than the control arm (Table 4.1) despite the number of clusters in the two arms being comparable. This was due to the variability in cluster size between the two arms which is liable to happen by chance in a cluster randomised trial; in this trial the three practices with very large cluster size were all in the intervention arm.

Figure 4.1: CONSORT trial flow diagram.

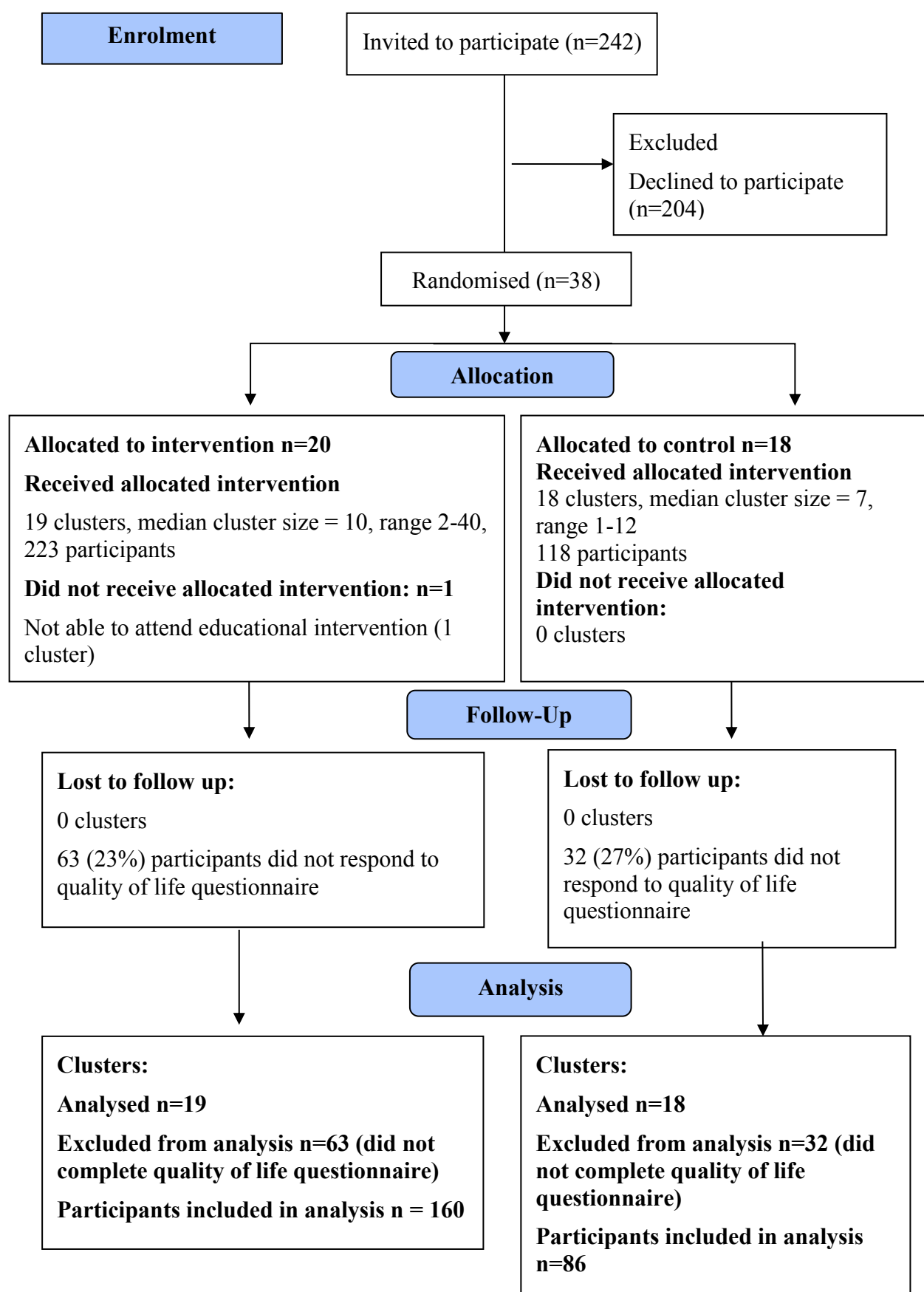
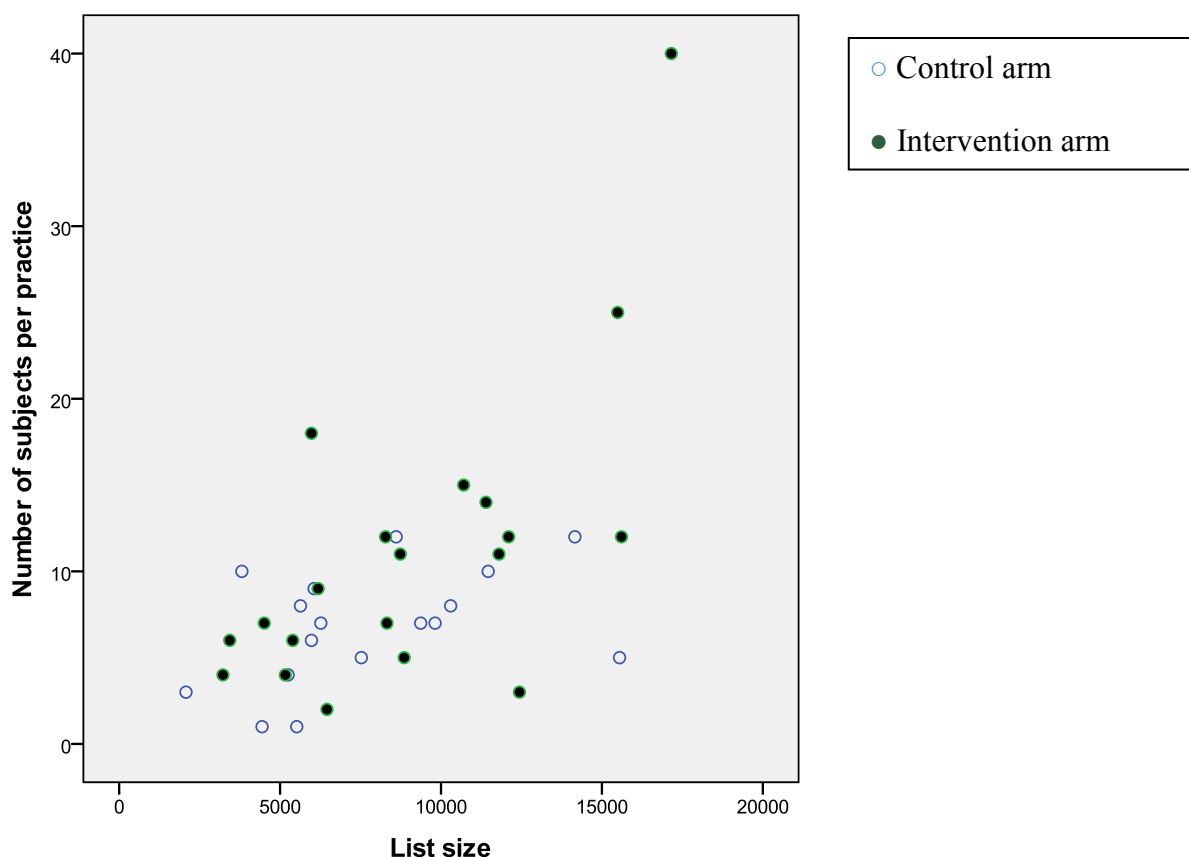


Figure 4.2 shows the cluster size variation between clusters, for example practice 15 (control arm) had a large list size and 37 eligible patients, but only five patients consented to take part, where-as practice 22 (intervention arm) had 40/108 patients consent to take part. Appendix 2 shows the number of patients in each arm who were eligible and invited to take part and how many of them actually did.

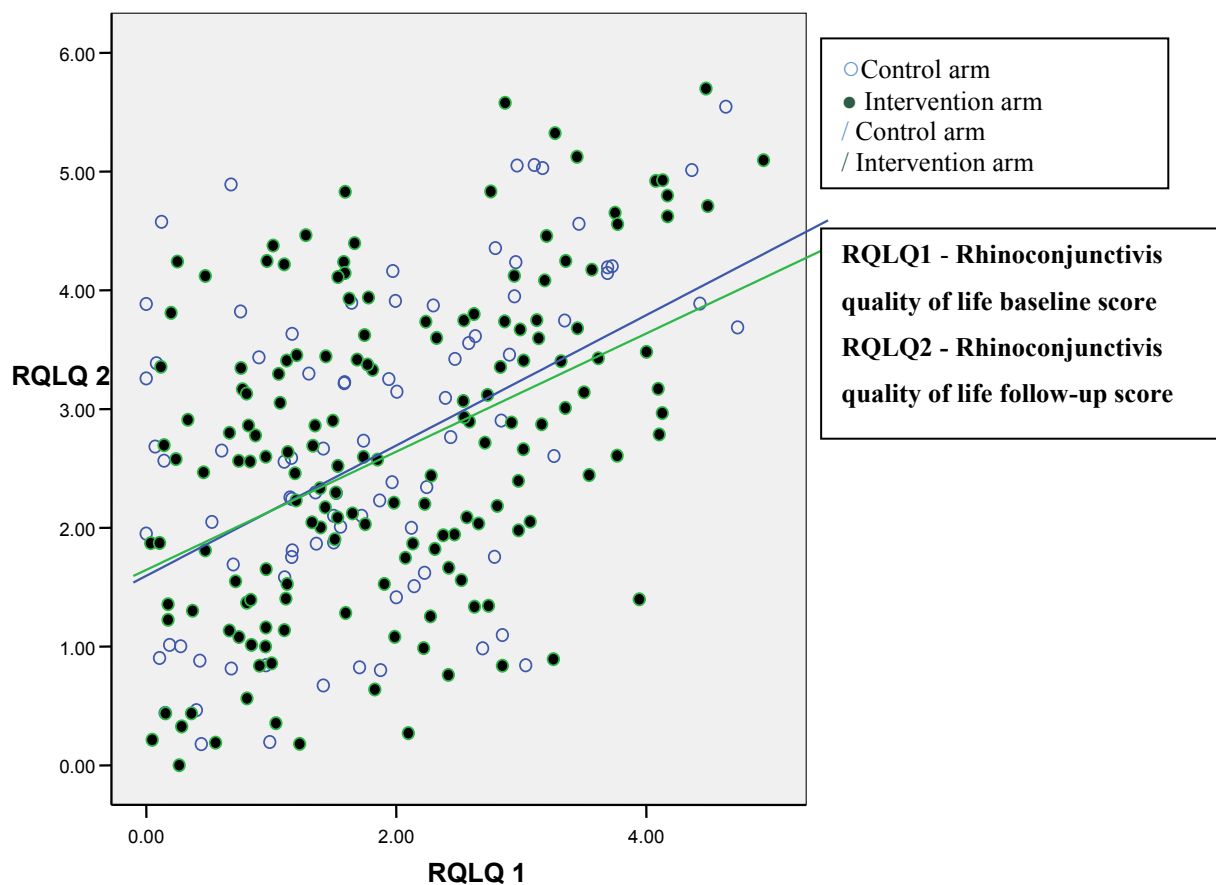
Figure 4.2: Variation in cluster size between intervention and control arms.



4.2. Primary outcome: RQLQ(S)

Adjusting for baseline RQLQ(S) in the analysis was based on an assumption that patients with a higher baseline RQLQ(S) score will have a higher RQLQ(S) at follow-up, which was measured at the peak of the pollen season. Figure 4.3 shows that baseline RQLQ(S) was strongly associated with follow-up RQLQ(S). The lines cross, which may indicate that at one point the intervention arm was doing worse than the control arm, however this was explicable by sampling error. Figure 4.3 presents unadjusted data and was not the model used in the analysis, it is purely indicative evidence for adjusting for baseline RQLQ(S), which was stated in the trial protocol prior to analysis (as per CONSORT guidelines (Campbell, Elbourne et al. 2004)).

**Figure 4.3: Association between baseline (RQLQ1) and follow-up (RQLQ2)
Rhinoconjunctivitis Quality of Life Questionnaire scores**



Two hundred and forty six out of 341 patients (72%; 50.2% male, mean age 15 years) provided complete data and were included in the primary outcome analysis. The effect of the intervention was to improve RQLQ(S), but not significantly (-0.15, 95% CI -0.52 to +0.21), meaning that the training had a small non-significant impact on disease-specific quality of life after adjusting for baseline RQLQ(S), practice list size, region, year of study and deprivation. The improvements in RQLQ(S) detected were well short of the minimal clinical important difference (0.5) (Juniper, Guyatt et al. 1994).

Repeating the same analysis without adjusting for baseline RQLQ(S) gave more patients (n=273), but was still not significant (-0.03, 95%CI -0.35 to +0.42).

Examination of the seven individual domains of the unadjusted RQLQ scores shown in Figures 4.4a-g firstly reinforces the fact that participants in this trial had mild-moderate hay fever, as no mean RQLQ(S) value was higher than 3.5 out of a score range of 0-6 (where 0 = no impairment of RQLQ(S) and 6 = high impairment of RQLQ(S)).

Secondly Figures 4.4a-g illustrate little evidence that there is a main effect of the intervention, or intervention with baseline RQLQ(S), the lines are not completely parallel, however this is explicable by chance. Figures 4.4 a-g show the unadjusted individual domain scores of the RQLQ(S), these data have not been subjected to multi-level modelling to take account of clustering, but as there was no intervention effect multi-level modelling analysis on each domain would not add to

the interpretation of the results. These figures are therefore only illustrative, but have the advantage of clearly showing the baseline and post-intervention minimum and maximum values of the mean domain scores and the change over time in each group. Although there are no apparently important differences between the intervention and control arm unadjusted RQLQ(S), it was important to explore whether any one domain was more affected by the intervention than another. Figure 4.4c and 4.4f show that the intervention arm's mean score for non-nose/eye symptoms and eye symptoms respectively were higher at baseline than the mean of the control arm, but at six weeks the two values were the same.

Figure 4.4a: RQLQ(S) scores recorded at baseline and 6 weeks post intervention for the activity domain.

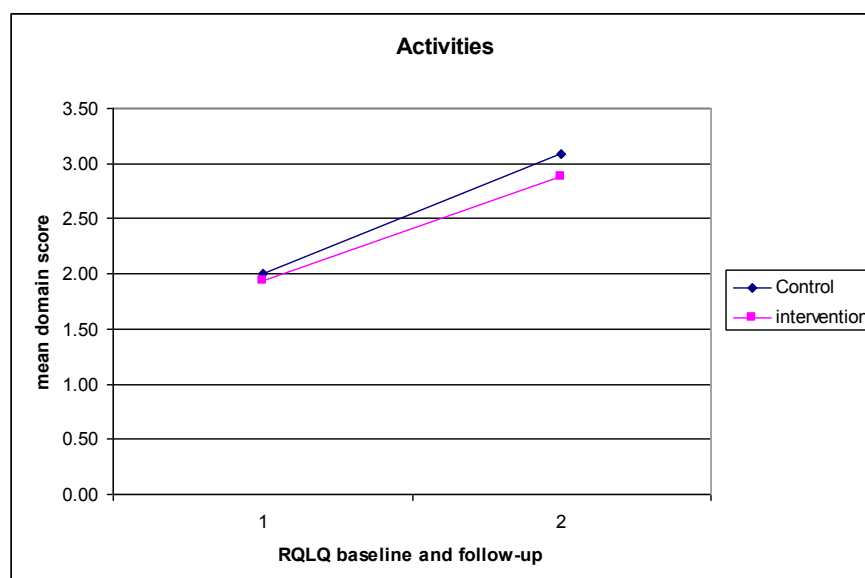


Figure 4.4b: RQLQ(S) scores recorded at baseline and 6 weeks post intervention for the sleep domain.

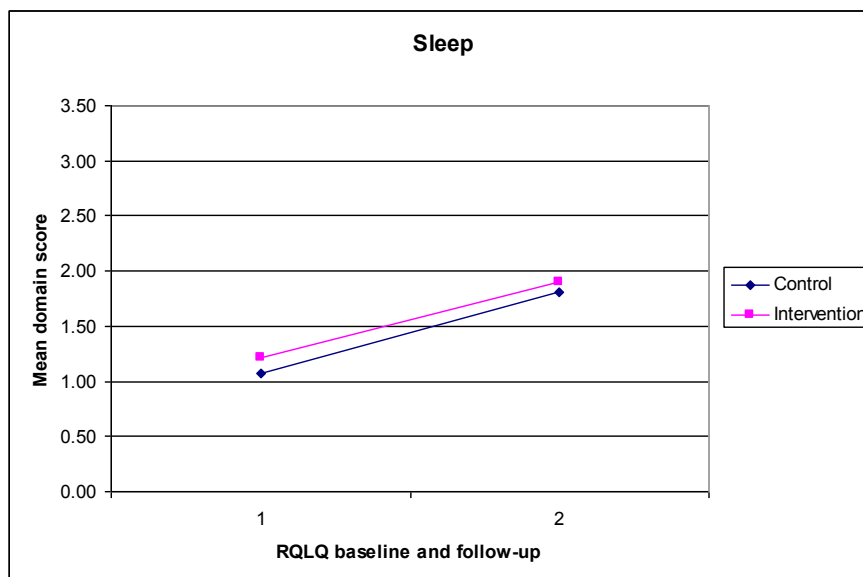


Figure 4.4c: RQLQ(S) scores recorded at baseline and 6 weeks post intervention for the non-nose/eye symptoms domain.

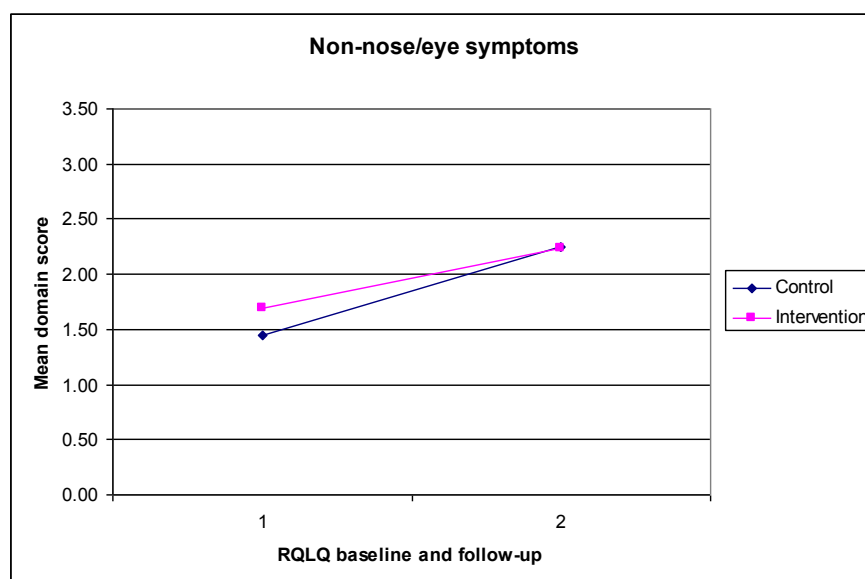


Figure 4.4d: RQLQ(S) scores recorded at baseline and 6 weeks post intervention for the practical problems domain.

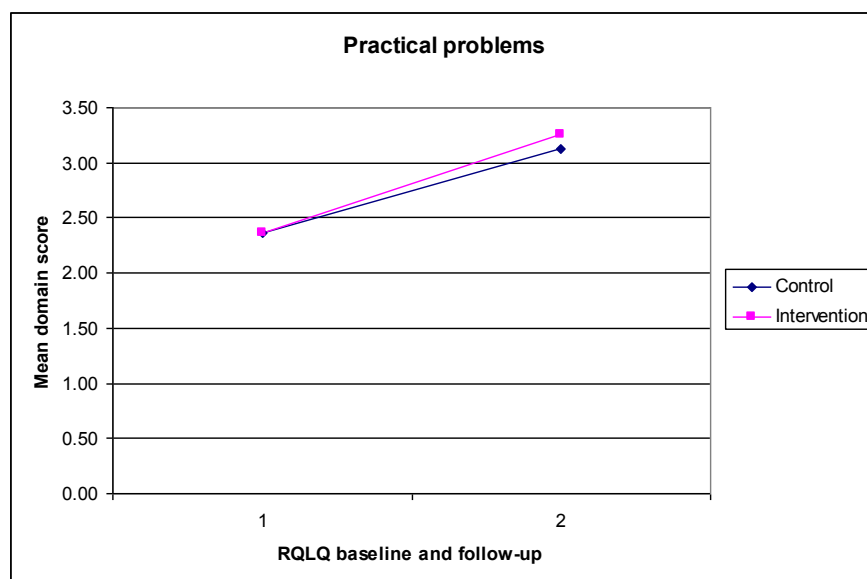


Figure 4.4e: RQLQ(S) scores recorded at baseline and 6 weeks post intervention for the nasal symptoms domain.

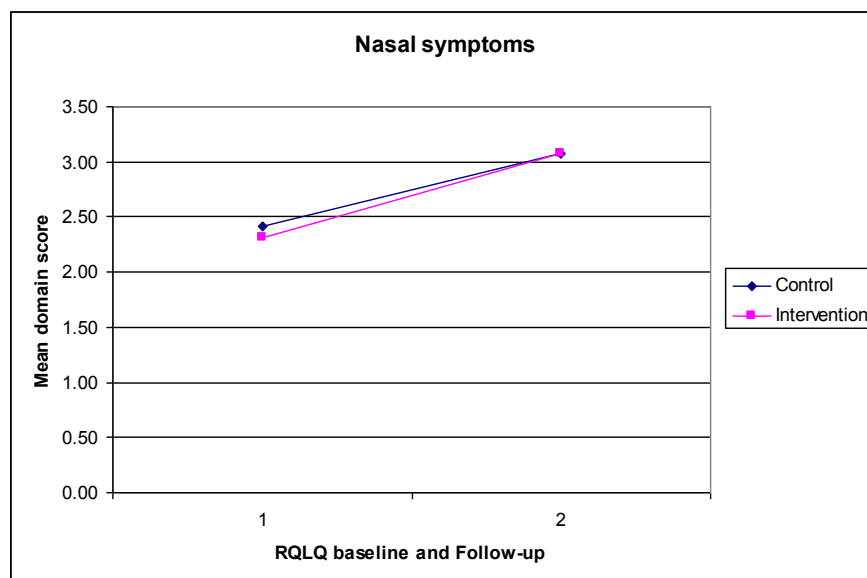


Figure 4.4f: RQLQ(S) scores recorded at baseline and 6 weeks post intervention for the eye symptoms domain.

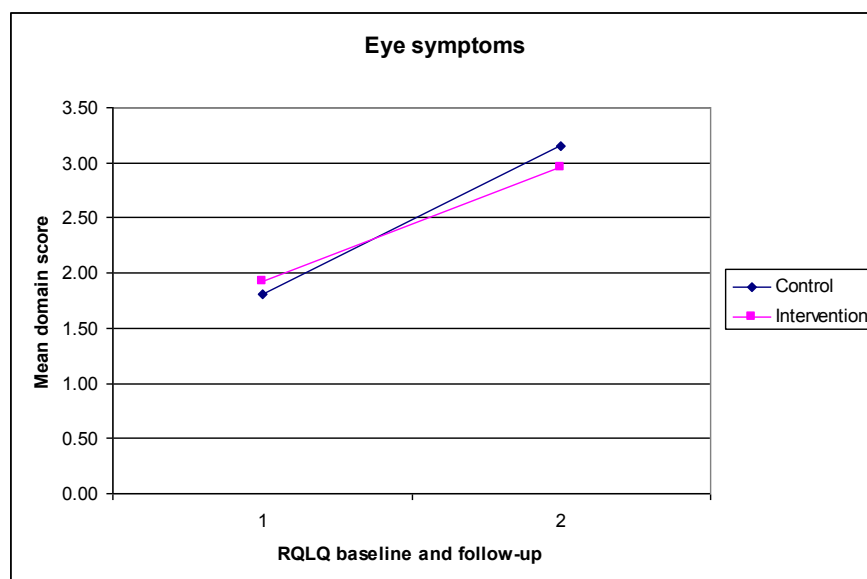
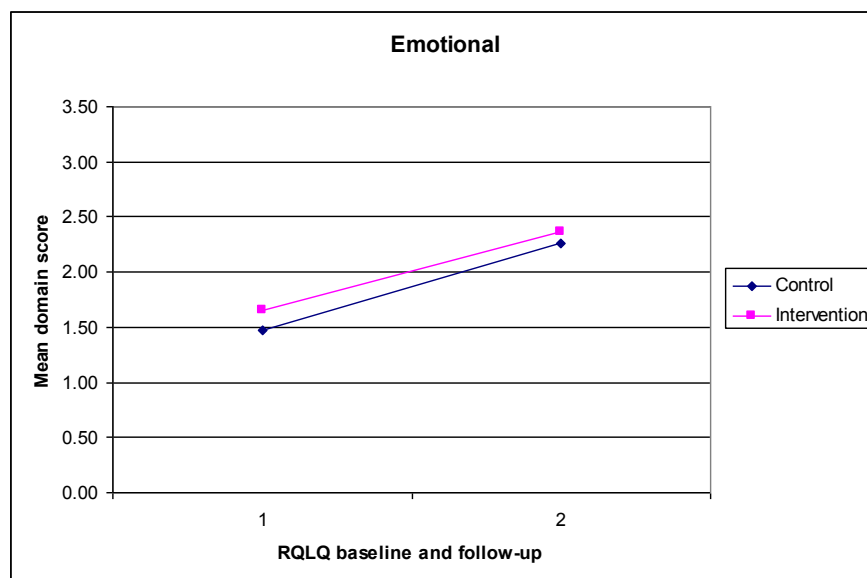


Figure 4.4g: RQLQ(S) scores recorded at baseline and 6 weeks post intervention for the emotional domain.



4.3. Secondary outcomes

4.3.1. Symptom scores

Symptom scores in the intervention arm were slightly lower than the control arm (-0.24, 95% CI -1.03 to +0.54).

4.3.2. Consultation and prescribing data

Five practices out of 38 did not provide data on consultation and prescribing patterns (three control and two intervention arm practices). One of these, a control practice, was not willing to provide data about consultations and prescriptions not related to hay fever and the remaining four did not respond to requests for data. There were no significant differences in the total number of consultations, number of consultations for allergic rhinitis or other respiratory conditions and total number of prescriptions for allergic rhinitis between the two arms (see Table 4.3); however the total number of prescriptions differed between the two arms. The mean total number of prescriptions per patient was 2.24 in the control arm and 2.89 in the intervention arm.

Table 4.3: Consultation and prescribing data

	Intervention arm (n = 193)	Control arm (n = 88)	Point estimate (95%CI)²
Total number of consultations ¹	200	85	+0.30 (-0.02, +0.63)
Total number of allergic rhinitis consultations	55	29	-0.08 (-0.24, +0.08)
Total number of consultations for other respiratory conditions	27	8	+0.11 (-0.01, +0.22)
Total number of prescriptions	557	197	+1.11 (+0.08, +2.15)
Total number of prescriptions for allergic rhinitis	406	140	+0.01 (-0.10, +0.12)

¹ from date seen to 31st August 2009 or 2010. ² 95% confidence limits for difference in mean between intervention and control arms

4.3.3. Assessment of change in clinical practice

Health care professionals' improvement in confidence, understanding and management markedly increased post-intervention when compared with the baseline assessment (see Table 4.4). All scores improved from Time 1 (immediately prior to the training day) to both Time 2 (immediately after the training day) and Time 3 (after all patients had been seen as part of the study), but there was little change between Times 2 and 3.

Table 4.4: Audit of confidence in delivering allergy care (n=21)

Question	Time 1*	Time 2*	Time 3*	Point estimate (95% CI) ¹
How confident are you at:				
Taking a comprehensive allergy history from a patient with suspected allergy?	2·6	4·2	4·4	1.6 (1·0, 2·2)
Doing skin prick testing?	1·1	2·7	2·4	1.5 (0·4, 2·6)
Ordering specific IgE test?	1·5	3·8	3·5	2.0 (1·2, 2·8)
Making a diagnosis of allergy?	2·1	4·4	4·3	2.2 (1·6, 2·7)
Explaining the various effective treatment strategies for allergic problems?	2·2	4·3	4·7	2.4 (1·9, 2·9)
Prescribing/recommending treatment for allergic conditions?	2·3	4·1	4·6	2.1 (1·4, 2·8)
Teaching patients how to use nasal spray devices?	2·3	4·7	5·0	2.5 (1·9, 3·2)
Explaining the causes and mechanisms of allergy?	2·4	4·2	4·5	2.1 (1·4, 2·7)
Understanding the impact of allergy on morbidity and mortality?	2·6	4·2	4·5	2.1 (1·4, 2·7)
How likely are you to do the following:				
Ask about other allergic symptoms (e.g. nose/skin) when assessing a patient with asthma?	3·3	4·8	4·8	1.3 (0·6, 2·0)
Consider total steroid use in patients on multiple therapies?	2·6	4·2	4·1	1.6 (1·0, 2·2)
Offer practical advice on avoiding allergens?	3·1	4·8	4·9	1.7 (1·0, 2·4)
Suggest patients use their nasal steroids regularly?	3·1	4·9	5·0	1.9 (1·3, 2·5)

*Time 1 – immediately prior to the training day, Time 2 – immediately after the training day, Time 3 – after all patients had been seen as part of the study (range 7-28

days). ¹ 95% confidence limits for change in mean score from time1 to time 3

4.3.4. Timing of primary and secondary outcome and grass pollen data

Grass pollen data were collected from two sites for 2009 and 2010. Figure 4.5 indicates that the grass pollen reached high levels (50-149 pgm^3) at both sites in both years. The protocol timeframe for data collection aimed for baseline RQLQ(S) and symptom scores in March 2009/2010, patients to be seen by their health care professional in May/June 2009/2010, and follow-up RQLQ(S) and symptom scores to be recorded in July/August 2009/2010 (Hammersley, Elton et al. 2010). Figure 4.6 shows the actual data collection timing in relation to the pollen count, and it can be seen that the timing of the baseline data collection slipped, with the majority of baseline RQLQ(S) and symptom score data in year one (RQLQ1 2009) being collected in May 2009, and a small number were not collected until June 2009. Baseline data collection in year two (RQLQ1 2010) was complete by the end of May 2010.

Figure 4.5: Pollen count in 2009/2010

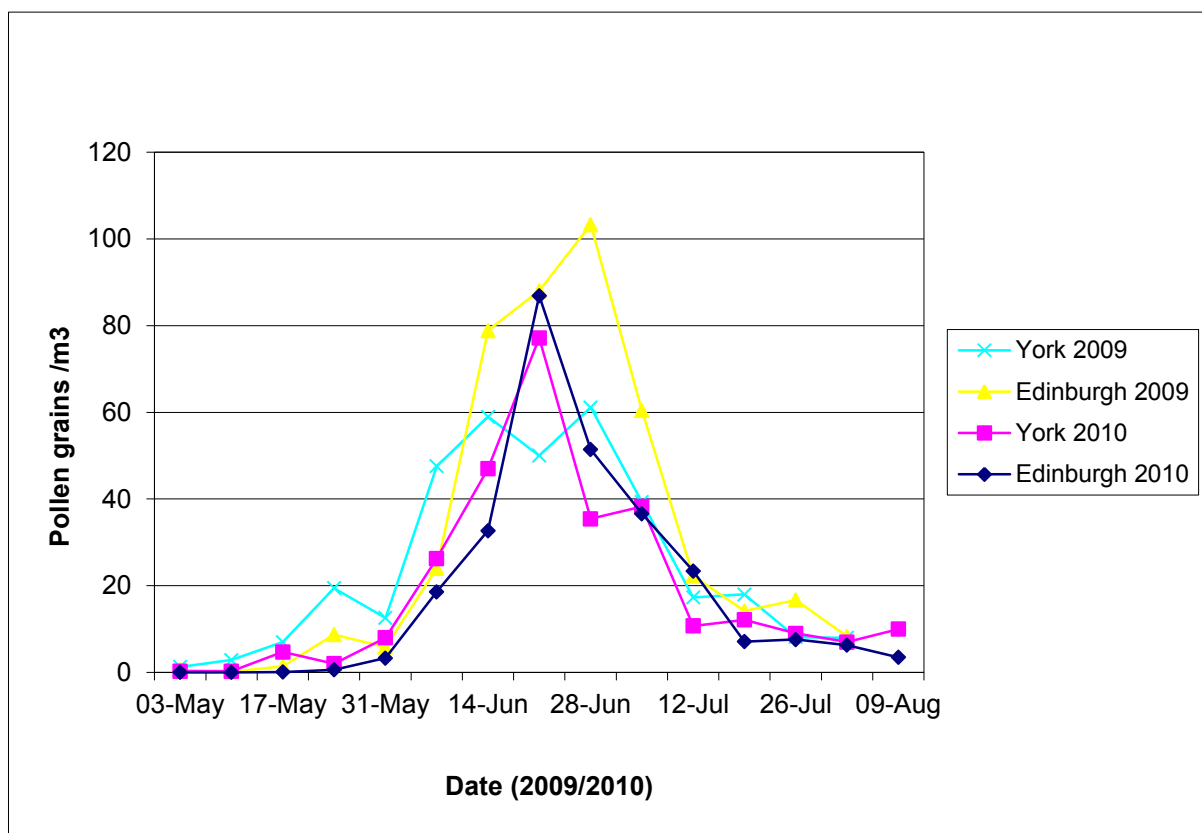
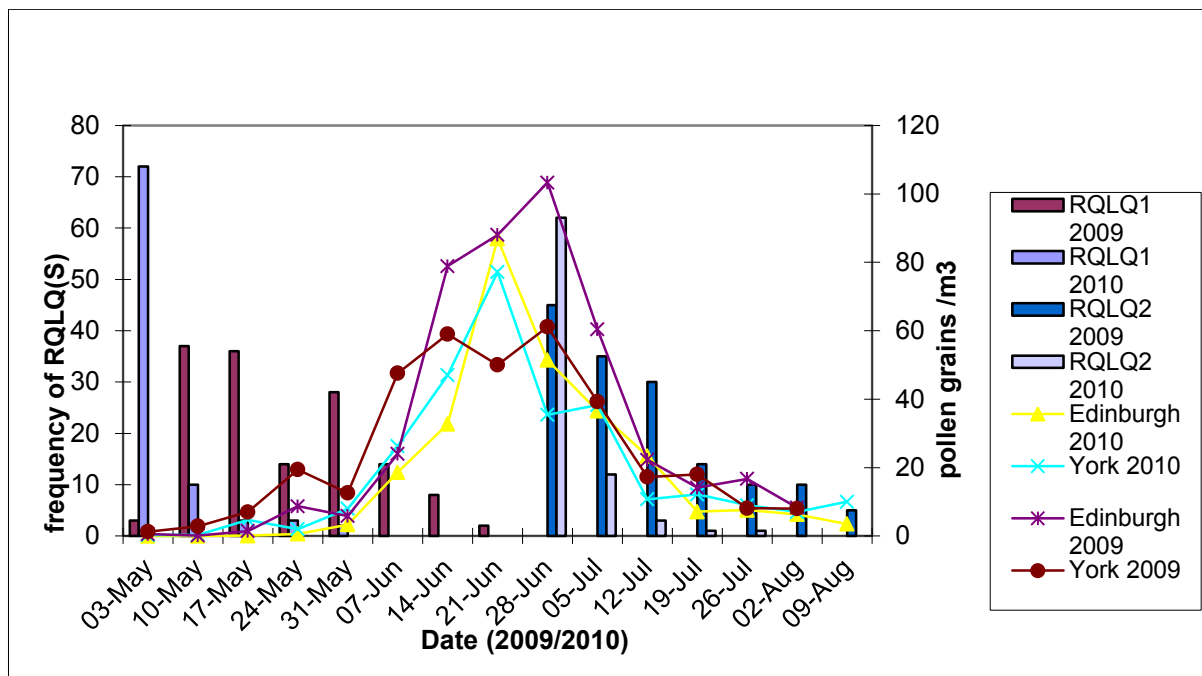


Figure 4.6: Relationship between pollen counts and RQLQ(S) data collection times



Notes: The pollen forecast is usually given as low (<30 pgm³), moderate (30-49 pgm³), high (50-149 pgm³) or very high (≥150 pgm³).

RQLQ1 – Standardised Rhinoconjunctivitis Quality of Life Questionnaire at baseline

RQLQ2 – Standardised Rhinoconjunctivitis Quality of Life Questionnaire at follow-up

4.3.5. ICC estimates

As discussed above, the estimate of the ICC in the adult study (Sheikh, Khan-Wasti et al. 2007) was negative (Table 4.5), and an F ratio of less than unity indicated that there was potentially less variation between practices than would be expected by chance. The estimates for ICC in this study using both methods described in Section 3.10.5 are shown in Table 4.5.

Table 4.5: ICC estimates using alternative approaches in two studies

	Mixed-model CI for ICC 95%	Bayesian interval for ICC 95%
Adult study	-0.143 to +0.012	0.002 to 0.0201
Adolescent study	-0.02 to +0.25	0.0016 to 0.145

4.4. Missing data

4.4.1. Patterns of missingness for the primary outcome RQLQ(S)

341 patients were allocated to either the intervention or control arm of whom 309 patients contributed with data on at least one occasion (baseline or follow-up or both). 282 patients had a baseline measurement, 273 patients had a measurement at six months follow-up and 246 patients had complete data at both time points. Patients in the intervention arm with some missing data had higher scores on the occasions when they are observed (Table 4.6a). The amount of missing data was roughly equal in the two treatment arms. As described in Section 4.9.5, a complete

case analysis provides unbiased estimates under the assumption that the missing data were missing completely at random, however the means estimated separately for each missingness pattern above suggest that this assumption may not hold.

Table 4.6a Patterns of missing data in the intervention arm

Pattern	n	Mean RQLQ(S) at baseline	Mean RQLQ(S) at follow up
Observed-observed	160	1.87	2.66
Observed-missing	24	1.96	N/A
Missing-observed	20	N/A	3.04
Total	204		

Table 4.6b Patterns of missing data in the control arm

Pattern	n	Mean at baseline	Mean at follow up
Observed-observed	86	1.80	2.68
Observed-missing	12	2.34	N/A
Missing-observed	7	N/A	1.93
Total	105		

Table 4.6c Patterns of missing data combined

Pattern	n	Mean at baseline	Mean at follow up
Observed-observed	246	1.85	2.67
Observed-missing	36	2.08	N/A
Missing-observed	27	N/A	2.75
Total	309		

Using the direct likelihood approach (Molenberghs and Kenward 2007), the estimated (adjusted) effect of the intervention on the outcome was 0.031 (s.e. 0.185; 95% CI: -0.33 to 0.39), compared with the primary analysis based on the complete cases: estimates effect: -0.154 (s.e. 0.182; 95% CI:-0.52 to 0.21). The overall mean effect of the intervention was estimated to be 0.058 (s.e. 0.185; 95% CI: -0.30 to 0.42). The two approaches to sensitivity analyses gave estimate effects of 0.212; (s.e. 0.214; 95% CI: -0.210 to 0.633) (poor outcome) and 0.025; (s.e. 0.209; 95% CI: -0.39 to 0.44) (good outcome).

Summary

Despite an improvement in the knowledge and understanding in the health care professionals which was sustained over the short-to-medium term, this did not result in a change in patient outcomes, evidenced by no difference between the two arms in prescribing for allergic rhinitis. The results of the cluster RCT have been reported in keeping with the CONSORT guidelines (Campbell, Piaggio et al. 2012), and are described in terms of clusters and patients, primary and secondary outcomes, process measures which will allow the effect of the intervention, or lack of effect to be explored, and ICC estimates are reported which will give helpful context to any future trials of educational interventions in primary care.

Chapter 5 - Discussion

This chapter will firstly consider the strengths and limitations of the trial undertaken and seek to interpret the findings of this work in the context of the wider literature of educational interventions in primary care, and secondly, present the conclusions and reflect on the implications for future work.

5.1. Statement of principal findings

This large primary care-based cluster RCT has shown that a short intensive evidence-based allergy workshop for health professionals led to substantial and short-medium term improvements in professionals' self-reported confidence and understanding of the management of hay fever. Despite this, it did not translate into changes in clinical practice in terms of frequency of consultations or prescribing habits. Most importantly, this did not lead to clinically significant improvements in disease-specific QoL or symptom scores in adolescents with hay fever.

5.2. Strengths and limitations of the evaluation

Educational interventions aimed at improving health care professionals' knowledge and changing patient's health outcomes should be evaluated for effectiveness and reported in the same way as any other intervention (Medical Research Council 2000; Campbell, Elbourne et al. 2004).

5.2.1. Strengths of the evaluation

The main strength of this trial was the decision formally to evaluate this evidence-based complex educational intervention using an adequately powered cluster RCT. A parallel group trial would have been inappropriate due the risk of contamination between patients randomised in the same practice. The use of cluster trials for

educational interventions in health care settings such as primary care is widely recommended (Eldridge and Kerry 2012). An important related strength of this trial was reaching the sample size required in terms of number of clusters and patients, which was made difficult in the first year due to low numbers of practices volunteering for the trial. By extending the trial to English sites and recruiting for a further year, adequate power was achieved (Hammersley, Elton et al. 2010), which is particularly important in the context of negative trials in order to minimise the risk of Type II errors (Kirkwood et al. 2003). Further explanation of the power calculations and the decision to continue into a second year of recruitment are described in Appendix 11.

The educational intervention evaluated in this trial was an adapted one-day short course which was regularly delivered by Education for Health for training health care professionals in primary care. The developmental work for the short course had already been completed by educationist/health care professionals at Education for Health during the development of the modules for the Diploma in Allergy. The allergy module was evaluated in the parallel group trial previously described (Sheikh, Khan-Wasti et al. 2007), and measured the effectiveness of this on a validated disease-specific quality of life measure (Juniper, Thompson et al. 1999). This was in keeping with the MRC's complex intervention framework (Craig, Dieppe et al. 2008). The educational intervention was modified a number of times in consultation with expert educationists using the best evidence available at the time (Scadding, Durham et al. 2008).

A range of relevant process measures, which aimed to shed light on the relevant mechanisms through which any changes were mediated and/or blocked, were chosen. Nested process evaluations can also provide insight into why a successful intervention works or can be optimised (Craig, Dieppe et al. 2008). Despite the acceptability of the intervention and its impact on professionals' self-assessed confidence and knowledge of hay fever management, the intervention appeared not to equip individuals with the ability to enact relevant structural changes in their practices to translate this into improvements in care processes.

Before an intervention can be utilised in routine care the strength of the evidence and its internal and external validity should be considered (Eldridge et al. 2008). Internal validity refers to the consideration of whether the observed effect of the intervention is actually due to the intervention itself and not due to the characteristics of the participants recruited to each arm or the way the outcome was measured (Eldridge and Kerry 2012). A well designed and conducted, blinded RCT of sufficient size should have high internal validity. Selection bias can occur if the people recruiting participants are aware of the participants allocation (Eldridge et al. 2009), as there is a chance that participants with a particular characteristic will be selected for recruitment; for example, in this trial participants in the intervention arm may have been selected on the basis of more severe hay fever compared with participants in the control sites, and this would obviously impact on the intervention effect and introduce bias. This trial was designed so that participants were identified and invited to take part before the cluster was randomised, which is quite straightforward for trials of management of chronic disease where searches of

the electronic record can be used to identify eligible participants, thus reducing the risk of selection bias. The consideration of selection bias contributes to the internal validity of the trial (Eldridge, Ashby et al. 2008). Recruitment of clusters in this trial was more pragmatic and as this group of general practices were self-selected in that they volunteered to take part and all were included, this may have affected the internal validity of the trial. Other measures of internal validity considered in this trial were: the effect of clustering in the sample size calculation and in the analysis; blinding of individual participants to allocation status and assessment of the primary outcome blind to allocation status (Eldridge, Ashby et al. 2008). Blinding of participants to allocation status raises an ethical issue with this cluster trial; it could be argued that fully informed consent is compromised by withholding allocation status from the participants, however Hutton (Hutton 2001) argues that one seeks consent to be in an experiment, not to consent to a particular treatment. The ethical and practical considerations of cluster trials create a tension which can only be judged on an individual basis. In this trial patients were unaware whether they were seeing a trained or untrained health care professional, but were able to opt out of the appointment and not complete the questionnaires as with any study.

Factors which affect the external validity of the study are whether there is a difference between the trial participants and the general population to which the results may be applied, or, between the intervention and how it was delivered in the trial and how it may be delivered in a routine setting (Eldridge and Kerry 2012). Again this can be influenced by good trial design - inclusion criteria for both

clusters and participants should not be limiting and exclusion criteria should be kept to a minimum. The inclusion and exclusion criteria (see Sections 4.5.3 and 4.5.4) were kept as simple as possible, however a general practitioner or practice nurse in each practice did screen the list of eligible participants prior to letters being sent, and the reasons for any exclusions were recorded (Appendix 2).

The trial was conducted under the supervision of an Independent Trial Steering Committee (Appendix 12) and conformed to the CONSORT checklist (Appendix 13). A detailed protocol which included a detailed analysis plan was developed and published (Hammersley, Elton et al. 2010) (see Appendix 14).

5.2.2. Limitations of the evaluation

Difficulties in recruitment of general practices to this cluster trial resulted in extended recruitment involving two cohorts of patients over two years. This introduced a variation in pollen count between the two years (see Figure 4.5, Section 4.3.4). Pollen counting was based on the available two sites: one in Edinburgh and one in mid-Yorkshire. The clusters were however distributed throughout Edinburgh, Borders and the north of England; these were therefore only proxy measures for pollen. The pollen counts were broadly similar in the two regions and reached a level which should have triggered hay fever symptoms in both years. In the multi-level modelling analysis of final RQLQ(S) adjusting for list size, area, year, baseline RQLQ(S), deprivation and intervention there was a highly significant year effect, indicating that the second year cohort of adolescents were more affected than the first year cohort. Figures 3.1 and Figure 4.6 shows the impact of recruitment difficulties on the timing of the data collection. Practice recruitment was staggered which

impacted when patients were invited/recruited/provided baseline data. Baseline QoL scores as seen in Figures 4.4a-g do not start at zero, however because of the association between baseline RQLQ(S) and follow-up RQLQ(S) shown in Figure 4.3, analysis was adjusted for baseline RQLQ(S).

The difficulty in recruitment of practices and the resulting loss of power for the trial are shown in Appendix 11. After the first year of recruitment follow-up primary outcome data were available from 180 patients in 23 clusters, however only 156 patients in 21 clusters returned both baseline and follow-up outcome data. Based on this evidence the following options were discussed with the Trial Steering Committee:

- Proceed with two analyses with the data already obtained:
 - 180 patients with final RQLQ (i.e. no adjustment for baseline RQLQ)
 - 156 patients with baseline and final RQLQ
- Do no analysis and repeat the study in 2010 to obtain sufficient numbers for at least 80% power.
- Carry out an interim analysis with a priori intervention effect levels to determine whether to proceed to further recruitment.

Deviations from a trial protocol have to be justified and extending the study into a further year had implications in terms of financial resources, variation in pollen patterns in the second year and its subsequent impact of hay fever and ability to recruit clusters and patients which had proved difficult in the first year. However this had to be considered against reporting the results of a complex educational intervention which would be underpowered and therefore difficult to interpret. The

Trial Steering Committee recommended proceeding for a further year despite the financial implications and possible variation in pollen patterns in order to report a fully powered cluster trial. The additional costs associated with extending for a further year were met by two grants I was able to secure from GlaxoSmithKline and The University of Edinburgh.

Figure 4.2 in Chapter 4 shows the extent of the imbalance in the cluster size – more practices in the intervention arm had larger cluster size, which impacted on the total number of patients in each arm; this resulted in almost twice as many patients in the intervention arm than the control arm despite the attempts to achieve balance through stratifying by list size. The power for the trial was calculated taking into account the clustered nature of the study, which has the effect of inflating the variance of estimates of intervention effects by the design effect (see Section 2.5.2). The formula used for calculating the design effect in a cluster RCT assumes that the clusters will be of equal size and if they are not then there is a loss of power (Eldridge et al. 2006). Methods are described to take into account the potential for unequal cluster size (Eldridge, Ashby et al. 2006), however variability was not anticipated and therefore no adjustment to the trial power was made. In hindsight, a more suitable stratification would have been by eligible adolescents with hay fever, or at least adolescents registered rather than total list size. The impact on the power of this imbalance was modest, and outweighed by the larger than required number of clusters (see Appendix 11).

The ICC estimate used in the sample size calculation was 0.02, which is a relatively low value based on the finding that there was no evidence of significant between-cluster variation in the previously discussed adult trial (Sheikh, Khan-Wasti et al. 2007). The larger the value of ICC the greater the loss of power due to the cluster design. Estimates of ICCs in educational interventions in primary care are infrequently reported, ICCs of other primary care interventions such as obesity management education (Moore, Summerbell et al. 2003) are generally around 0.05. We were able to report ICCs using two approaches: a mixed model analysis of variance and Bayesian approach (see Section 4.3.5). The Bayesian method, which makes explicit quantitative use of external evidence for analysis (Spiegelhalter et al. 2000) guarantees an estimate for ICC of between 0 and 1. Despite the adequate sample size in this trial, the confidence limits were quite wide (see Table 4.5), which makes it difficult to predict the ICC value with any certainty for future studies. Cluster trials should always quote confidence limits for ICCs rather than just estimates (Turner et al. 2006), and even with the confidence limits, this may cause some difficulty in planning further studies, because sample size estimates depend on assumptions about the magnitude of ICC that cannot always be made with any certainty.

Simple and multiple imputation methods have been described in relation to QoL data (Fielding, Fayers et al. 2008; Sterne, White et al. 2009; Wang et al. 2009) and considered in relation to complete case analysis bias, which was the chosen method of analysis in this study. The justification for complete case analysis was based on the power required for the trial being achieved. Only 246/341 patients were included in the complete case analysis, which represents a substantial loss to follow-up. A

post-hoc sensitivity analysis was therefore undertaken. This was however a deviation from the analysis plan described in the protocol, which can affect the integrity of the results of RCTs. Despite this, when taking account of the missing data under a MAR assumption (see Section 4.4) there is still no evidence of a beneficial effect of treatment on the outcome variable RQLQ (S). This finding was confirmed in the two alternative scenario analyses: (1) assuming that patients with missing data have very poor outcomes; and (2) assuming that patients with missing data have very good outcomes.

A further limitation of this study may be that patients in the control arm of the cluster RCT consulted with a health care professional. It was necessary to design the study this way in order to understand the cause of any potential effectiveness of the educational intervention and to be able to distinguish this from any impact of simply being seen by a health care professional for hay fever. Control arm practices received an algorithm for the management of hay fever produced by Education for Health. One way of disentangling this issue would have been to include a third arm in which practices received no intervention, however this was not possible because of time and resource constraints.

Consideration should be given to the cost-effectiveness of any intervention as this is important for decision-makers in the health service. In a review of 51 educational interventions in primary care, only two gave any approximate costs for their intervention (Freudenstein and Howe 1999). Actual costs for the trial are detailed in Appendix 15. The cost of running the trial per practice in Scotland was £390, and in

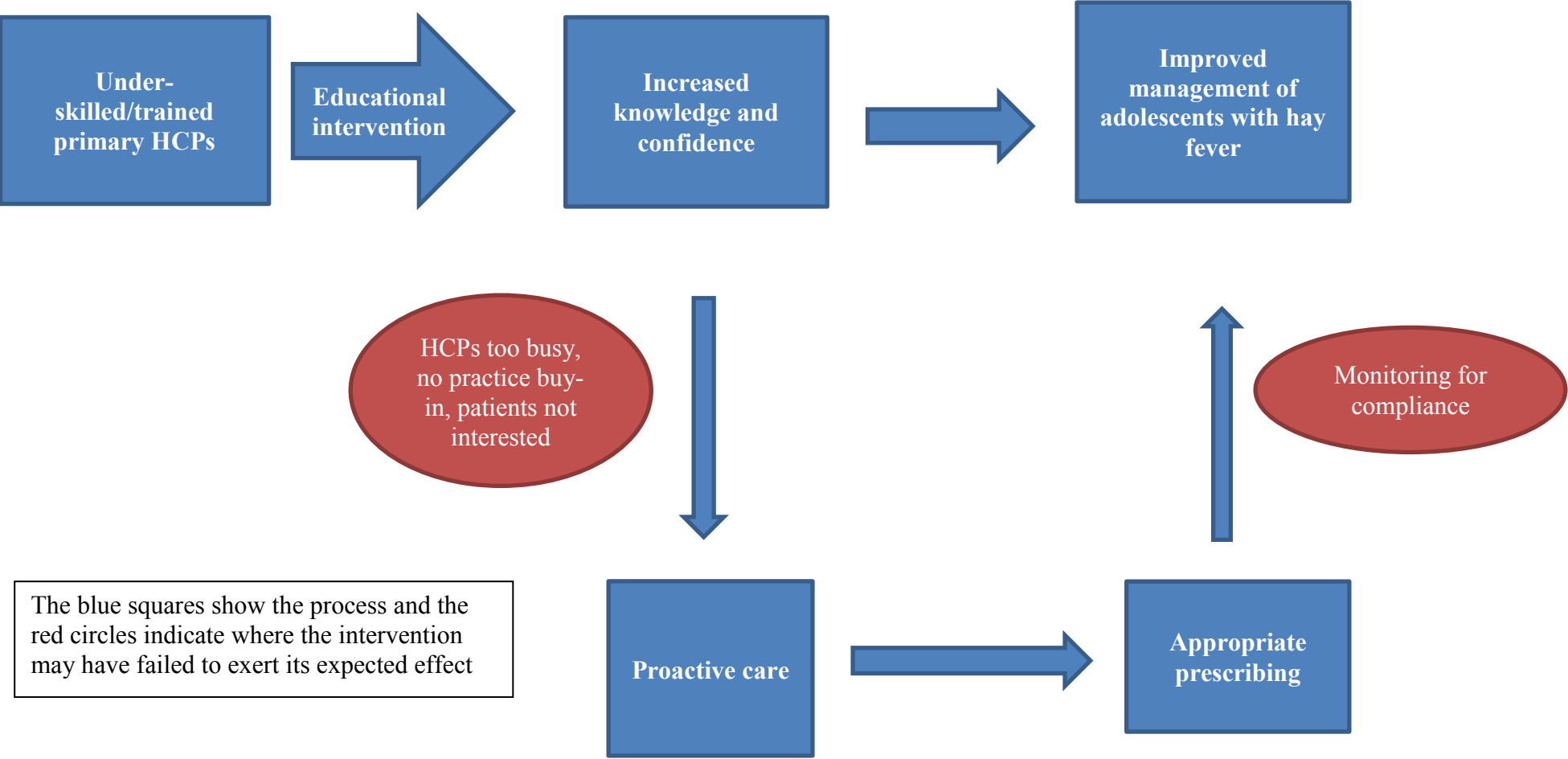
England £539, this cost was met by Health Boards and PCTs in each area from service support budgets and paid directly to each practice. The total cost for the 38 practices was £19439. This covered all the costs incurred in considering the trial, running the trial in each practice, attendance at the one day training and seeing the patients once in clinic. The training days themselves cost £4790, giving a total estimate of the cost of the trial of £24229. Per practice total cost was approximately £637. This does not include any researcher costs. These figures give an indication of actual costs for running the cluster trial in primary care; however it does not give any indication of cost-effectiveness, and comparative data of actual costs rather than cost-effectiveness are not reported in the literature. No economic analysis was included in this trial, again due to resource and time constraints. This limits the usefulness of trial findings for others to consider replication or use of the intervention on a wider scale.

There was no qualitative work embedded in this trial, which is becoming increasingly common when evaluating complex interventions in order to explore causal pathways of the intervention (Cresswell, Sadler et al. 2012). A recent successful example of a mixed-method approach is described by Cresswell et al, where a large cluster randomised trial of a complex pharmacist intervention was complemented by an embedded qualitative inquiry (Cresswell, Sadler et al. 2012). This paper supports the value of qualitative evaluation methods in complimenting RCTs of complex interventions and may have helped to interpret the negative findings of this trial, as the results of qualitative work can give insight into the blocks in the intended pathway. Figure 5.1 shows how the intervention was intended to exert

its effect on patient outcomes via education of untrained health care professionals. The blue squares show the process and the red circles indicate where the intervention may have failed to exert its expected effect. The educational intervention had the desired effect of improving self-assessed knowledge and confidence of the health care professionals; however it is unclear why this did not translate into improved outcomes for the patients without interviews with health care professionals or the patients.

Despite practices agreeing to take part in the trial, it may be that the trained health care professionals were unable to use their knowledge effectively due to time pressures in a busy practice, or that they were not encouraged/supported by other practice team members. Despite potential problems with building extra clinics into an already busy schedule, all patients who completed the baseline data were seen by their health care professional, but this does not mean that they complied with the recommendations given to them in terms of optimum medication strategies and adherence. An additional limitation of the study was therefore the lack of monitoring for compliance in the patient group.

Figure 5.1 Proposed causal map



5.3. Interpretation of the findings

5.3.1. Influence of the trainers on the intervention

Key dimensions of complexity relevant to this trial are behaviours required of those delivering and receiving the intervention; specialist trainers experienced in clinical practice as well as the delivery of evidence-based practice developed and delivered a short intensive course to health care professionals who then went on to see patients with hay fever and tried to alter their behaviour in terms of management of their own symptoms.

The two trainers were experienced, practicing allergy and respiratory nurses, with their own clinical knowledge and experience (Freudenstein and Howe 1999) which may have influenced their interpretation of guidelines and existing evidence. Both trainers discussed and modified the content of the one day course on a number of occasions before it was finalised and delivered, focussing on areas of particular importance for adolescent hay fever sufferers, and these repeated discussions would hopefully ensure consistent delivery of the materials by both trainers.

5.3.2. Influence of the health care professionals on the intervention

Practice health care professionals will also bring their own clinical experience and knowledge to any research study, and one of the main challenges of an educational intervention in any health care setting is to try to change clinical behaviour in-line with the best research evidence. The health care professionals were working within a local clinical context, where particular prescribing patterns may be enforced, and in this particular case where hay fever may not be considered a serious clinical

condition, possibly as it is not part of the Quality and Outcomes Framework (National Institute for Health and Clinical Excellence). Allergic rhinitis is a common co-morbidity in patients with asthma, and if left untreated can lead to poor asthma control (Scadding et al. 2012), a large retrospective cohort study showed that asthma patients with allergic rhinitis had more visits to their GP and were significantly more likely to be hospitalised compared with asthma patients without allergic rhinitis (Price et al. 2005). Subsequently the ARIA guidelines recommend that people with asthma are assessed for allergic rhinitis and vice versa (World Health Organization Initiative, Bousquet J et al. 2001). The NICE Quality Standard 5 (National Institute for Health and Clinical Excellence 2013) for asthma does include assessment of co-morbidities for adults, although allergic rhinitis is not specified. A systematic review of educational meetings, which includes short courses, found that the impact of such educational interventions may be smaller for outcomes that health professionals may perceive as not having serious consequences for the patient (Forsetlund et al. 2009).

The development-evaluation-implementation process proposed in the MRC guidance on complex interventions (Craig, Dieppe et al. 2008) includes identifying the existing evidence and a feasibility/piloting stage. When considering the use of the short course as the educational intervention for the trial, a limitation was the lack of consultation with health care professionals about how it might be most effectively delivered in terms of preferences for style of delivery such as workshops with interaction, educational outreach visits or audit and feedback (Thomson 1998). A systematic review of studies of interventions to improve

delivery of health care systems showed that dissemination activities alone resulted in little or no change in behaviour, however more complex interventions only produced moderate effects, and suggests that a range of interventions could lead to provider behaviour change (Oxman, Thomson et al. 1995; Forsetlund, Bjørndal et al. 2009). The MRC complex intervention guidance (Craig, Dieppe et al. 2008) suggests that it is crucial to develop a theoretical understanding of the likely process of change, and although the educational intervention was modified from a previously successful model (which was developed in consultation and collaboration with multi-professional stakeholders at the time), consultation with ‘stakeholders’, in this case the primary health care professionals targeted by the intervention may have been beneficial. In a survey of current allergy provisions and training (Levy et al. 2004), GPs expressed their preferred training option which included day long evidence-based taught courses. Exploration of practical barriers to implementing the guidelines introduced in the intervention could have been explored with health care professionals in a focus group setting and then suggestion of how to effectively address these included in the course. Training only one member of a large team of health care professionals may not be sufficient to influence any managerial or policy structures that may be in place and in addition to the one day course a dissemination event for the whole practice may have supported the intervention.

5.3.3. Influence of the patients on the intervention

Patients in this study had on average relatively mild impairment of QoL measured by the RQLQ(S), which is in line with a similar study exploring quality of life of perennial rhinitis sufferers (Sheikh, Khan-Wasti et al. 2007). Patients were

recruited from a primary care setting, using a clinician diagnosis of hay fever or a prescription for drugs used in nasal allergy in the last two years, rather than objective evidence of moderate or severe disease. As also observed in the perennial rhinitis trial (Sheikh, Khan-Wasti et al. 2007), the impact of this training intervention may have been more evident if trial entry had been restricted to those with more severe disease. This would however have reduced the generalisability of the intervention to everyday general practice.

The adult trial showed a modest improvement in disease-specific quality of life among patients with perennial rhinitis compared with usual care (Sheikh, Khan-Wasti et al. 2007). Differences between the one day intensive course used in this trial and adult diploma study are likely to relate to sustained effort and the incentive of succeeding in a final exam than necessarily the content of the day. Short courses are popular, they are easily accessed with relatively little burden on the practice in terms of time out of clinical practice and they represent the preferred mode of continuing professional development in some groups (Thomson 1998). They may serve to signpost people to best practice, but not necessarily inform people enough to make changes to their clinical practice, and may highlight education need, and provide opportunities for networking, meeting experts and bringing people together.

If the training workshop had achieved a sustained change in clinical practice there would have been more consultations in the intervention arm. This was not evident, although patients in the intervention arm did receive more prescriptions compared with the control arm. The training days were delivered by practicing health care professionals and based on current evidence-based guidelines for the management

of hay fever developed by the BSACI (Scadding, Durham et al. 2008). The prescribing data collected included all repeat prescriptions; therefore if the intervention practices followed the guidance given during the course, patients with persistent symptoms should have received an antihistamine, nasal steroid and eye drops as appropriate.

5.4. Conclusions and implications for future work

In conclusion, this intensive hay fever training course for primary care health care professionals was found acceptable and increased self-assessed confidence in attendees, but this did not translate into improvements in symptom control or quality of life of adolescents with hay fever. Future trials need to build on the findings of both this and the adult perennial rhinitis trial (Sheikh, Khan-Wasti et al. 2007), and find ways of equipping participants of such short courses with the skills necessary to bridge the gap between knowledge and day-to-day practice. Such evidence is needed to help ensure that the NHS and other health systems internationally invest their limited resources in evidence-based education of proven effectiveness.

The findings of this cluster trial and the parallel-group adult RCT (Sheikh, Khan-Wasti et al. 2007) both point to the need for further work in improving the knowledge and skills of primary health care professionals. The two varying models are extreme: an intensive one day course and a six month diploma course requiring a large time commitment to on-line learning and assessment. It could be argued that the best educational intervention may lie somewhere between the two models, for example blended learning courses, which have become increasingly feasible with wider access and greater functionality/versatility offered by the Internet, however

further exploratory work is needed before any resource could be put into testing this. Systematic reviews of educational interventions are inconclusive, but suggest that a blended learning approach may be more effective at changing patient outcomes (Grimshaw, Shirran et al. 2001). This needs to be explored with educationists, health care professionals and policy makers using qualitative approaches before a new model for an educational intervention could be developed.

It would be equally helpful to talk to the target group about the usefulness of consultations about the management of their hay fever. It was assumed that an educational intervention for health care professionals followed by a consultation was acceptable for the adolescents; however other methods of communicating with this patient group could be explored, such as reminders about medication and adherence use via social media, information about pollen counts direct to mobile phones, and this could be explored using discussion forums either in person or again using social media.

The guidance for developing and evaluating complex interventions describes a cyclical process (Craig, Dieppe et al. 2008), however on reflection only the evaluation of this educational intervention followed this guidance. When designing a complex intervention such as an educational course, it should be developed to the point where it can reasonably expect to have an effect. As we adapted an existing course being delivered to health care professionals rather than developing a new course, this was not the case. In addition there was no pilot work, on the basis that the six month diploma evaluation had been successfully completed in a primary care

setting (Sheikh, Khan-Wasti et al. 2007). These assumptions weakened the likelihood of the short course impacting patient outcomes. Any future iteration should include identifying the evidence base for the likely process of change (Craig, Dieppe et al. 2008), which as discussed above could include the views of relevant stakeholders and exploration of existing literature, as well as qualitative process evaluation to explore causal mechanisms and an economic evaluation to aid possible implementation.

5.5. Personal reflections and lessons learnt

I conclude this thesis by offering some personal reflections. With the benefit of hindsight I would have approached a number of elements of this trial differently. In the very first discussions with the CSO the issue of recruitment in primary care, particularly to cluster trials was highlighted. Previous experience of primary care research has taught me that personal contacts can go a long way in engaging practices in research; however experience from this trial suggests that the subject area has to be pertinent and seen to be of clinical importance and in the case of hay fever this appeared to be a stumbling block. In discussions with practices during the recruitment phase, a number of GPs told me that hay fever in adolescents was not a clinically important area for them to focus resources and therefore engage in research. This proved a problem when evaluating an educational intervention aimed at primary health care professionals. Alternative recruitment approaches could have included recruiting pharmacists to attend the training, and adolescents as they present for their over the counter medication, this approach was being piloted (Porteous et al. 2013) at the time of the current trial and the results are awaited. Earlier discussion

with a larger number of primary care research networks would have helped with the recruitment, the extension into England brought additional costs for the trial, but improved recruitment enormously.

No matter how rigorously a trial is designed, if the intervention being evaluated is weak, there is unlikely to be an intervention effect detected. This trial aimed to evaluate if an ‘off-the-shelf’ one day workshop for health care professionals could improve the quality of life of adolescents, and in hindsight this is not the way forward. It is a fact that NHS staff attend one-day courses as part of their professional development, but this can only be used as a signpost to more intensive learning. This trial would have benefitted from greater investment in the development of the educational intervention, including qualitative work to explore the potential causal pathway of the intervention using the MRC’s complex interventions framework (Craig et al. 2008).

The trial would have been strengthened with a health economics arm, as this would have contributed to the literature for future educational intervention evaluations. In future trials I would engage very early with a health economist to incorporate an economic evaluation of the intervention.

In terms of future cluster trials in primary care this trial contributes further evidence for ICC assumptions for sample size calculations, which will be useful when planning trials in primary care. The recruitment difficulties experienced and described will help future planning of trials in terms of practice and participant

recruitment and retention and indicating the resources required for cluster trials in primary care.

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"Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: case-control study." J Allergy Clin Immunol 120(2): 381 - 387.

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Appendices

Appendix 1: Ethical, research and development approval

Approval letter from research ethics committee



Lothian NHS Board

Deaconess House
148 Pleasance
Edinburgh
EH8 9RS
Telephone 0131 536 9000
Fax 0131 536 9009
www.nhslothian.scot.nhs.uk



Lothian Local Research Ethics Committee 02

Telephone: 0131 536 9061
Facsimile: 0131 536 9346

16 September 2008

Miss Victoria Hammersley
CSO Research Training Fellow
University of Edinburgh
General Practice Section, University of Edinburgh
20 West Richmond Street
Edinburgh
EH8 9DX

Dear Miss Hammersley

Full title of study: Cluster randomised controlled trial of an educational intervention for healthcare professionals into the management of school-age children with hayfever
REC reference number: 08/S1102/37

Thank you for your letter of 27 August 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Sub-Committee of the REC held on 24 September 2008.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

- **Please remove the question Mark in paragraph 2 of the consent form for 12 to 15 year olds, and forward a copy for our files.**

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.



Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Application	1	10 July 2008
Investigator CV		10 July 2008
Protocol	6	10 July 2008
Covering Letter		10 July 2008
Letter from Sponsor		20 May 2008
Compensation Arrangements		20 May 2008
Questionnaire: RQLQ(S)	Validated	
Letter of invitation to participant	1	10 July 2008
GP/Consultant Information Sheets	1	10 July 2008
Participant Information Sheet: Parents/ Guardians	4	27 August 2008
Participant Information Sheet: 16-18 Years	4	27 August 2008
Participant Information Sheet: 12-15 Years	4	27 August 2008
Participant Consent Form: 12-15 Years	3	27 August 2008
Participant Consent Form: Practices	1	10 July 2008
Participant Consent Form: 16-18 yrs	2	10 July 2008
Response to Request for Further Information		27 August 2008
A Sheikh CV (Supervisor)		28 June 2008
GP Invitation Letter	1	10 July 2008

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

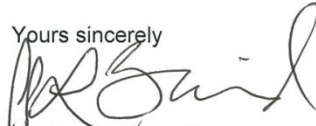
The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/S1102/37**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely



Professor Peter Hayes
Chair

Email: lyndsay.baird@nhsllothian.scot.nhs.uk

Enclosures: "After ethical review – guidance for researchers"
Site approval form

Copy to: Elspeth Currie

Approval letter for substantial amendment from research ethics committee

Lothian NHS Board

Lothian Research Ethics Committee
02
Deaconess House
148 Pleasance
Edinburgh
EH8 9RS
Telephone 0131 536 9000
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Miss Victoria Hammersley
CSO Research Training Fellow
General Practice Section, University of
Edinburgh
20 West Richmond Street
Edinburgh
EH8 9DX

Date 11 December 2008
Our Ref
Enquiries to Lyndsay Baird
Extension 89061
Direct Line 0131 536 9061
Email lyndsay.baird@nhslothian.scot.nhs.uk

Dear Miss Hammersley

Study title: Cluster randomised controlled trial of an educational intervention for healthcare professionals into the management of school-age children with hayfever
REC reference: 08/S1102/37
Amendment number: 1
Amendment date: 19 November 2008

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 28 November 2008.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Questionnaire: Healthcare Professional Process Outcomes	7	19 November 2008
Questionnaire: Overall Assessment of Hayfever	7	19 November 2008
Questionnaire	Visual Analogue Scale - 7	19 November 2008
Protocol	7	19 November



Headquarters
Deaconess House 148 Pleasance Edinburgh EH8 9RS
Chair Charles J Winstanley
Chief Executive James Barbour O.B.E.
Lothian NHS Board is the common name of Lothian Health Board

		2008
Participant Information Sheet: Practices	7	19 November 2008
Participant Information Sheet: 12-15 Years	7	19 November 2008
Participant Information Sheet	(16-18 Years) 7	19 November 2008
Participant Consent Form: Practices	7	19 November 2008
Participant Consent Form: 12-15 Years	7	19 November 2008
Participant Consent Form: managing your Hayfever	7	19 November 2008
Flowchart for participants	7	19 November 2008
Education for Health Short Course programme	7	19 November 2008
Information for randomised controlled trial	7	19 November 2008
Patient data collection form		
Practice Data collection Form	7	19 November 2008
Notice of Substantial Amendment (non-CTIMPs)	1	19 November 2008
Letter of invitation to participant	7	19 November 2008
GP/Consultant Information Sheets	7	19 November 2008
Covering Letter		19 November 2008
Participant Information Sheet	Parent - 7	19 November 2008

R&D approval

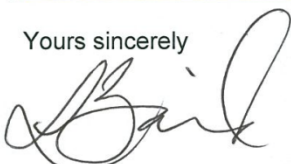
All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/S1102/37:	Please quote this number on all correspondence
---------------------	---

Yours sincerely



Miss Lyndsay Baird
Committee Co-ordinator

E-mail: lyndsay.baird@nhslothian.scot.nhs.uk

Copy to: *University of Edinburgh*

Lothian research and development approval letter

University Hospitals Division
Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ



Lothian

RESEARCH & DEVELOPMENT

Room E1.12

Tel: 0131 242 3330

Fax: 0131 242 3343

Email: R&DOffice@luht.scot.nhs.uk

Director: Professor Heather A Cubie

HAC/JB/approval/2f

21 August 2008

Ms Victoria Hammersley
CSO Research Training Fellow
Edinburgh University, General Practice Section
20 West Richmond Street
Edinburgh
EH8 2DX

Dear Ms Hammersley

MREC No: N/A
LREC No: 08/S1102/37
R&D ID No: 2008/P/GP/21
Title of Research Cluster randomised controlled trial of an educational intervention for healthcare professionals into the management of school-age children with hayfever
Protocol No/Acronym: Research Protocol Version 6 dated 12 August 2008

The above project has undergone an assessment of risk to NHS Lothian and review of resource and financial implications. I am satisfied that all the necessary arrangements have been set in place and that all Departments contributing to the project have been informed. The documents reviewed are listed at the end of this letter.

I note that this is a single centre study and that Co-Sponsorship between the University of Edinburgh and NHS Lothian has been discussed and appropriate responsibilities agreed.

On behalf of the Chief Executive and Medical Director, I am happy to grant management approval from NHS Lothian to allow the project to commence, subject to the approval of the appropriate Research Ethics Committee(s) having also been obtained. You should note that any substantial amendments must be notified to the relevant Research Ethics Committee and to R&D Management with approval being granted from both before the amendments are made.

This letter of approval is your assurance that NHS Lothian is satisfied with this project. For approved research, NHS Lothian will provide cover for negligence for NHS and Honorary clinical staff for research associated with their clinical duties. It is not empowered to provide non-negligent indemnity cover for patients. Cover for healthy volunteer studies is the personal responsibility of both NHS and honorary employees and is usually arranged with a medical defence organisation or through the University of Edinburgh.

As Chief Investigator or local Principal Investigator, you should be fully committed to your responsibilities within the Research Governance Framework for Health and Community Care, an extract of which is attached to this letter.

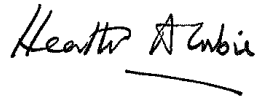
List of Reviewed Documents

Document	Version	Date
Rec Parts A&B Signed by Chief Investigator		
Locked Site-Specific Information Form signed by Principal Investigator	C/131376/212563/1	10/07/2008
Sponsorship Letter		20/05/2008
CV of Principal Investigator		

"Improving health through excellence and innovation in clinical research"

Protocol	V6	12/08/2008
Invitation Letter - Practices	V1	12/08/2008
Invitation Letter – Practice Nurse	V1	12/08/2008
Patient Information Sheet – 12-15 Years	V3	12/08/2008
Patient Information Sheet – 16- 18 Years	V3	12/08/2008
Patient Information Sheet – Parents/Guardians	V3	12/08/2008
Patient Information Sheet – General Practices	V1	12/08/2008
Consent Form –16-18 Years	V2	12/08/2008
Consent Form – 12-15 Years	V2	12/08/2008
Consent Form - Practices	V1	12/08/2008

Yours sincerely



Professor Heather A Cubie
R&D Director

enc Research Governance Certificate ☐ (to be signed and returned)
 Tissue Policy (if applicable) ☐
 MTA (if applicable) ☐ (to be signed and returned)

cc Administrators, Research Ethics Committee

"Improving health through excellence and innovation in clinical research"

Lothian research and development amendment approval letter

University Hospitals Division

Queen's Medical Research Institute
47 Little France Crescent, Edinburgh, EH16 4TJ

TM/SG/app-lrecamend

12 January 2009

Ms Victoria Hammersley
General Practice Section
University of Edinburgh
20 West Richmond Street
Edinburgh
EH8 9DX



Lothian
Director: Professor David Newby
RESEARCH & DEVELOPMENT OFFICE
Room E1.12
Tel: 0131 242 3330
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Email: R&DOffice@luht.scot.nhs.uk

Dear Ms Hammersley

LREC No: 08/S1102/37
R&D Project ID No: 2008/P/GP/21
Title of Research Cluster randomised controlled trial of an educational intervention for healthcare professionals into the management of school-age children with hayfever

I am writing in reply to recent correspondence in relation to the following amendment(s) to the above project.

Amendment: No: 1 dated 19 November 2008

1. *To extend recruitment to Grampian, Fife, Forth Valley, Tayside, Greater Glasgow, North of Tyne, County Durham and Tees Valley, Darlington, North Yorkshire and York*
2. *Addition of a third (non-randomised) control arm*

- *Protocol V 7 dated 19 November 2008*

We have now received a copy of the amendment(s) and assessed any consequential changes in NHS Lothian resource use. I confirm that NHS Lothian management approval is extended to cover the specific changes intimated. You should be aware that approval for this amendment must also be received from Lothian Research Ethics Committee before it is implemented

Yours sincerely

Dr Tina McLelland
R&D Governance Manager
Direct Tel: 0131-242-3340
Email tina.mclelland@nhs.net

"Improving health through excellence and innovation in clinical research"

Additional English site research and development approval letters



County Durham

County Durham & Tees Valley Primary Care Trusts'
Research Management & Governance Unit
County Durham PCT
John Snow House
University Science Park
Durham
DH1 3YG

Tel: 0191 301 1300
Fax: 0191 3744100
Safehaven Fax: 0191 374 4102
www.countydurhampct.nhs.uk

Our ref: RE-MM483
Your ref:

12 February 2009

Direct Line: 0191 374 4211
Reception: 0191 374 4103
Email: richard.errington@nhs.net

Miss Victoria Hammersley
CSO Research Training Fellow
General Practice Section
University of Edinburgh
20 West Richmond Street
Edinburgh
EH8 9DX

Dear Miss Hammersley

**Cluster randomised controlled trial of an educational intervention for
healthcare professionals into the management of school-age children
with hayfever**

**REC No: 08/S1102/37
R&D No: 392**

The Research Management & Governance Unit of County Durham & Tees Valley Primary Care Trusts gives **approval** for this project to begin in **Darlington PCT, County Durham PCT, Middlesbrough PCT, Redcar & Cleveland PCT, Stockton on Tees tPCT and Hartlepool PCT** subject to the following conditions:

- Approval from the Research Ethics Committee with site-specific approval where appropriate.
- Honorary Contracts have been issued where relevant.
- Any Accidents and Complaints related to the research are reported to the PCT(s) and RM&G Unit through the usual systems.
- Serious Adverse Events affecting local patients are reported to the PCT(s) and RM&G Unit promptly.
- The RM&G Unit is provided with copies of any updated documentation after NRES approval and before it is implemented
- The Researchers will provide assistance with any Monitoring or Audit requests from the RM&G Unit or the PCT(s).
- The research will not require any financial support from the PCT(s), unless there is a written agreement to the contrary.
- The PCT(s) and RM&G Unit are informed when the project ends.

Best wishes in your research.

Yours sincerely

R. Errington

Richard Errington
RM&G Unit Lead

Copy to:

Annette Waites, Kirsty Hesketh & Kevin Garrigan Co Durham PCT
Sue Goulding, Darlington PCT
Marie Clark, Stockton on Tees tPCT and Hartlepool PCT
Peter Kelly, Middlesbrough PCT and Redcar & Cleveland PCT

Telephone enquiries, please contact:
Name; Linda Dobrzanska
Email: Linda.dobrzanska@nhsleeds.nhs.uk
Telephone: 0113 2033473 / 0795806828



22nd February 2010

Stockdale House
Headingley Business Park
Victoria Road
Leeds
LS6 1PF
www.nhsleeds.nhs.uk

Miss Victoria Hammersley
CSO Research training Fellow
University of Edinburgh
General Practice section
20 West Richmond Street
Edinburgh
EH8 9DX

Ref No: P/0045

Dear Vicky

Re: Cluster randomised controlled trial of an educational intervention for healthcare professionals into the management of school-age children with hay fever.

Thank you for your recent submission to NHS Leeds requesting governance approval for the above study.

Following consideration of your submission I am pleased to confirm that research management and governance approval has been granted by NHS Leeds for the above research to take place as described in your application and accompanying documentation.

Conditions of approval

You should be aware that approval is granted subject to the conditions specified below:

- In undertaking this research you must comply with the requirements of the Research Governance Framework for Health and Social Care (2nd edition 2005) which is mandatory for all NHS employees.
- Consent for NHS Leeds to audit your project, which is implicit in your acceptance of approval.
- Where any amendments, substantial or non substantial are made throughout the course of the study these should be notified to NHS Leeds.
- A copy of the final study report should be forwarded to NHS Leeds.
- Should any serious adverse event(s) occur throughout the course of the study these should be notified to NHS Leeds using the contact details set out above.
- You comply with NHS Leeds Policies on the handling of data. These policies are available from the research manager.

Chair: Linda Pollard OBE

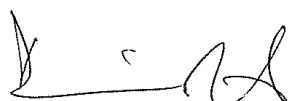
Chief Executive: John Lawlor

Leeds Primary Care Trust is the registered name of NHS Leeds
NHS Leeds is a smokefree organisation

Should you require any clarification regarding any of the points raised above, or have any further queries in relation to approvals and post approval study management process then please do not hesitate to contact me on 0113 3057607.

Finally, may I take this opportunity to wish you well with your study and look forward to hearing about your progress in due course.

Yours sincerely



Damian Riley
Executive Director of Primary Care (Medical Director)

Approved documents

The documents reviewed and approved by NHS Leeds are listed as follows

<i>Document</i>	<i>Version</i>	<i>Date of Document</i>
REC Form	v.2.5	
SSIF	v.2.5	
Participant Information Sheet		
Parents and guardians	v.5.0	31/12/09
Young people aged 16 – 18	v.5.0	31/12/09
Young people aged 12 - 15	v.4.0	31/12/09
Consent Form:		
16 – 18 year old	v.3.0	31/12/09
12 -15 years	v.4.0	31/12/09
CV of researcher		Document reviewed
CV of academic researcher (if applicable)		n/a
Sponsor identified		Sponsor identified
Indemnity identified		Indemnity identified
Protocol	v.6.0	31/12/09

Chair: Linda Pollard OBE

Chief Executive: John Lawlor

Leeds Primary Care Trust is the registered name of NHS Leeds
NHS Leeds is a smokefree organisation



NHS North of Tyne

Research & Development
NHS North of Tyne
Bevan House
1 Esh Plaza
Sir Bobby Robson Way
Great Park
Newcastle upon Tyne
NE13 9BA

Tel: (0191) 217 2783
Fax: (0191) 217 2505

19 February 2009

Project No: **09C MISC 001**

Ms Victoria Hammersley
CSO Research Training Fellow
University of Edinburgh
General Practice Section
20 West Richmond Street
Edinburgh
EH8 9DX

Dear Ms Hammersley

Re Cluster randomised controlled trial of an educational intervention for healthcare professionals into the management of school-aged children with hayfever

Thank you for sending the information about the above project. As the Lead Organisation for Research Management & Governance (RM&G) I am pleased to give approval for the above study to take place in primary care in:

- North Tyneside PCT
- Newcastle PCT
- Northumberland Care Trust
- South Tyneside PCT
- Sunderland TPCT
- Gateshead PCT.

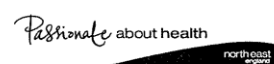
Please accept this letter as verification of our support for your project.

This project has been registered on the PCT's research database and you should keep the R&D team informed of any progress on a regular basis. This will allow the database to be kept up to date. In addition, we also have an obligation to monitor at least 10% of all research studies undertaken in our area and the database is used to identify such projects. Should your project be randomly chosen for monitoring, the R&D Team will contact you.

In particular, it is a condition of our support that the R&D Team **must** be notified of:

- commencement and completion of the study;
- any significant changes to the study design;
- any changes to research teams and any changes in the circumstances of researchers that may have an impact on their suitability to conduct research (eg. employment status, registration status, criminal record etc.)

Working on behalf of Newcastle and North Tyneside
Primary Care Trusts and Northumberland Care Trust



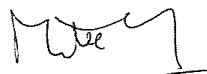
- any decision made by a Research Ethics Committee regarding this study, including a copy of your ethics approval letter;
- any serious adverse effects on participants or staff. Please note that guidance of what constitutes an adverse event is available on the R&D website. (www.northtynesidepct.nhs.uk/rdnet1)
- any suspension or abandonment of the study;
- all funding, awards and grants pertaining to this study, whether commercial or non-commercial;
- all publications and/or conference presentations of the findings of the study.

In line with national policy, the PCT will not give approval for any NHS research work which does not comply with Research Governance guidelines. (*The Research Governance Framework for Health and Social Care* is available from the DoH website). If Honorary Contracts are required, these will be issued separately.

The principal investigator is required to send a final report and a lay summary to the PCT within three months of the completion date of the research project.

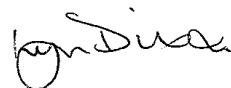
Commencement of any work related to this study, using resources or premises of primary care organisations in Northumberland, Tyne & Wear, implies agreement with the above conditions.

Yours sincerely



Dr Mike Guy

Medical Director, NHS North of Tyne, Bevan House, 1 Esh Plaza, Sir Bobby Robson Way, Great Park, Newcastle upon Tyne NE13 9BA



Lyn Dixon

Director of Service Modernisation/Executive Nurse
NHS North of Tyne, Bevan House, 1 Esh Plaza, Sir Bobby Robson Way, Great Park, Newcastle upon Tyne NE13 9BA

Copies to: Claire Kelly, Clinical Audit/R&D Facilitator, South Tyneside PCT

North and East Yorkshire Alliance R&D Unit

Main Office: Learning and Research Centre
York Hospitals NHS Foundation Trust
York
YO31 8HE

Project reference: NYY-P01359
Ethics ref: 08/S1102/37

Miss Victoria Hammersley
General Practise Section
20 West Richmond Street
Edinburgh
EH8 9DX

Tel: (01904) 726996
Fax: (01904) 731297

www.northyorksresearch.nhs.uk

09/04/2009

Dear Miss Hammersley

Research Governance Approval

Project: Cluster randomised controlled trial of an educational intervention for healthcare professionals into the management of school-age children with hayfever

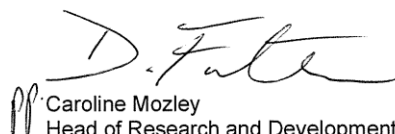
Thank you for submitting details of this project for Research Governance Approval by NHS North Yorkshire and York

On behalf of the Trust I confirm that the project can go ahead subject to assessment by the appropriate Ethics Committee. If you have not already done so, please supply me with a copy of the Ethics Committee's letter, either confirming its favourable ethical opinion or that full ethical review is not required.

Please note that as Chief Investigator for a "No Local Investigator" project you will be responsible for ensuring that the project is conducted in accordance with the Protocol, any Ethics Committee requirements, the Department of Health's *Research Governance Framework for Health and Social Care* (www.dh.gov.uk/assetRoot/04/10/89/65/04108965.pdf), the NHS Confidentiality Code of Practice (www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf) and any applicable legislation.

I would be grateful if you could send details of any publications and conference presentations that arise from this research for inclusion in our audit of research activity in due course.

Yours sincerely


Caroline Mozley
Head of Research and Development
On behalf of NHS North Yorkshire and York

cc:CLRN

The R&D Service for: East Riding of Yorkshire Primary Care Trust
Hull Teaching Primary Care Trust
Scarborough and N. E. Yorks Health Care Trust

Harrogate and District NHS Foundation Trust
North Yorkshire and York Primary Care Trust
York Hospital NHS Foundation Trust

Appendix 2: Reasons for exclusion from trial

Practice	No. of adolescents with hay fever	Exclusions with reasons	Invitations sent out	Reminders	No. of consenters
1	16		16	15	1
2	22		22	17	7
3	66	3 – mental health, serious hospital controlled, terminal illness in family	63	63	10
4	21		21	18	10
5	22	2 – family problems, learning difficulties	20	16	6
6	20		20	16	4
7	58		58	52	11
8	34		34	26	12
9	30		30	30	6
10	50		50	41	14
11	30		30	25	7
12	21	1 – autistic child	20	20	1
13	56		56	55	7
14	57		57	56	7
15	37		37	35	5
16	26		26	25	2
17	33		33	31	8

18	64		64	53	12
19	81	1 – Downs syndrome	80	66	25
20	31		31	25	8
21	40		40	0	12
22	108		108	98	40
23	18		18	16	3
24	58		58	49	12
25	58		58	51	18
26	60		60	55	12
27	41		41	38	6
28	32		32	27	7
29	39	11 – mental health or not current SAR as determined by lead GP	28	35	9
30	52		52	49	5
31	65		65	56	15
32	19		19	16	4
33	41		41	37	4
34	27		27	25	5
35	46		46	43	11
36	31		31	29	3
37	57		57	50	9
38	16		16	15	3
TOTAL			1565	1374	341

Appendix 3: Patient invitation letter

*Patient invitation letter from practice nurse
On Surgery letter headed paper*

Ref: Invitation to take part in important local research into teenage hayfever

Dear *(Patient Name)*

I'm writing to ask if you will join me in taking part in important new research into teenage hayfever? It's being carried out by the Allergy Research Group at Edinburgh University in our area this summer and is being funded by the Scottish Government. I'm one of 27 nurses taking part. I'm asking you if you'd like to be one of 300 teenagers (age 12-18 yrs) with hayfever who also get to take part.

You'll see from the poster and information sheet that researchers have already shown that teenagers are particularly affected by hayfever. Also that there's a clear link between teenage exam performance and hayfever.

The Research Group want to see if there is also a link between how well teenagers manage their hayfever, with the level of hayfever knowledge and skills their health professional has. And therefore, would you be able to control your hayfever better if your nurse had had special hayfever training?

I know that some of the teenagers I see at the surgery sometimes struggle to concentrate during hayfever season or even to play sports. I'm taking part because if successful, this research could be used to help plan better hayfever services in the NHS, helping more nurses get special hayfever training and therefore helping improve the lives of more teenagers with hayfever, possibly even their exam performance.

If you're interested, have a read of the poster and information sheet and share them with your parents or guardian. They need to know what's involved in the research too. Then fill in the consent form and reply slip and send it to Vicky, who is the researcher I am working with, in the envelope provided. If you want to talk to Vicky before deciding, then you can contact her on 0131 6503234/07969 775912 or you could email her at vicky.hammersley@ed.ac.uk

Part of my role is to run a special hayfever clinic this summer. Hopefully I'll see you there?

Regards

Practice Nurse name

Appendix 4: Information sheets

DO TEENAGERS' HAYFEVER SYMPTOMS IMPROVE IF THEY ARE TREATED BY HEALTH PROFESSIONALS WITH SPECIFIC HAYFEVER KNOWLEDGE AND SKILLS?

A Teenage Hayfever Research Study organised by the University of Edinburgh's Allergy and Respiratory Research Group and funded by the Scottish Government

Participant Information Sheet- Year 1

Information for teenagers, your parents or guardians



The Scottish Government, University of Edinburgh, and education charity Education for Health are trying to find out if teenage hay fever sufferers are able to control their hay fever symptoms better and so improve their quality of life, if they are treated by health professionals who have had specific evidence based hay fever training. Or not.

We needed nurses from 27 General Practices to agree to take part. We've sent you this information *because one of them is a nurse from your practice. All 27 are helping us find 300 teenagers (age 12 – 18 years) who have hay fever to also take part.* If we can't find 300 teenagers then we can't do the research. This sheet explains more about the research and what it means to take part. If you'd like even more information or have any questions which are not covered here, call Vicky Hammersley on 0131 6503234/07969 775912 or you can email her at vicky.hammersley@ed.ac.uk

Why this research is important?

Important research shows that hay fever affects up to 40% of children. Teenagers are particularly affected with symptoms including sneezing, itching and nasal blockage. Lots of teenagers are unable to play sports or concentrate on their schoolwork when their hay fever is bad to the extent that it can impact on their exam performance. We want to see if giving

specific hay fever training to nurses and doctors will result in improvements to their teenagers' hay fever – and potentially their exam performance.

Why you are being asked to take part, and what's involved?

We are asking you to take part because you have hay fever and are the right age. We know this because we are working with a nurse from your General Practice who has searched the medical records of all the patients registered there to identify teenagers who have hay fever.

She will be inviting you to attend one special hay fever clinic this summer to discuss your hay fever. We will ask you to fill out one short questionnaire before you go and to fill out two more after you have been. Your clinic appointment should last about 15 minutes, the same amount of time as each questionnaire will take to complete. Taking part therefore requires a total of one hour of your time this summer, but it's an hour that could end up improving the lives of thousands of teenagers with hay fever and potentially improving their exam performance.

What happens next if you decide to take part?

The first thing to do is to fill in the consent form and reply slip and send it back to Vicky Hammersley, the lead researcher on this study. The consent form asks for your permission for us to ask your doctor what medication you have been prescribed or recommended in the past and how often you have visited the practice during previous hay fever seasons. We won't collect or record any medical information not related to your hay fever. The form will also ask your permission to collect your exam data from the Education Authority for one year. Once you have sent the form back to Vicky she'll send you the first questionnaire or give you details on how to fill it in on the internet. The questionnaire asks how your hay fever is affecting your life right then, what symptoms you are having at the time, what medication you are taking to help you and how your hay fever this year compares with previous years.

Next your nurse will invite you to attend her special hay fever clinic once in the summer. Here you'll talk about your hay fever and things you could do to make you feel better and control your symptoms. Half of the nurses taking part will have had their special training before they run their clinic and half will have their training at the end of the study.

Then Vicky will ask you to fill out the questionnaire twice more at particular times. She'll be able to remind you to do this by texting, emailing or ringing you, whichever you choose. Your involvement starts in March and finishes in September.

Benefits of taking part

As well as this being a unique chance for you to take part in an important research study, we hope you will notice that you are better able to control your hay fever symptoms this summer.

If you don't want to take part

If you don't want to take part you don't have to. You don't need to give a reason and it won't affect the care you get from the health service. If you do decide to take part you are still free to change your mind at any time, also without giving a reason.

What happens to the results of the study?

If you take part we will send you a summary of the results. Since we hope to show a link between specialist training and improved patient health we will also tell doctors about the results to help them with their work. We'll do this by publishing our findings in a report to the Scottish Government's Chief Scientist Office and in medical journals. We expect that the findings will be used in planning future allergy services within the NHS.

Whose study is it?

The Allergy and Respiratory Research Group at Edinburgh University's Centre for Population Health Sciences is undertaking a programme of research with the aim of improving the delivery of care to patients with allergic disorders. This study has been funded the Scottish Government's Chief Scientist Office and will run until the end of October 2009. It has been approved by the Lothian Research Ethics Committee.

If you need more information or have questions

Please do contact lead researcher Vicky Hammersley who will be pleased to answer any questions about the study, you can contact her on 0131 6503234/07969 775912 or vicky.hammersley@ed.ac.uk

Or you can contact Dr Allison Worth (PhD):

Research Fellow, Allergy & Respiratory Research Group, Centre for Population Health

Sciences: GP Section, 20 West Richmond Street, The University of Edinburgh, EH8 9DX. Tel: 0131 6509463 or email: allison.worth@ed.ac.uk

Thank you for reading this information. We hope you'll take part in this important research study.

Take a step toward taking part, contact Vicky Hammersley on:

Direct line 0131 6503234
Mobile 07969 775912
Email vicky.hammersley@ed.ac.uk

Or write to her at: Allergy and Respiratory Research Group, Centre for Population Health Sciences: GP Section, The University of Edinburgh, 20 West Richmond Street, Edinburgh EH8 9DX

Participant Information Sheet- Year 2

DO TEENAGERS' HAYFEVER SYMPTOMS IMPROVE IF THEY ARE TREATED BY HEALTH PROFESSIONALS WITH SPECIFIC HAYFEVER KNOWLEDGE AND SKILLS?

A Teenage Hayfever Research Study organised by the University of Edinburgh's Allergy and Respiratory Research Group and funded by the Scottish Government

Information for teenagers & your parents or guardians



The Scottish Government, University of Edinburgh, and education charity Education for Health are trying to find out if teenage hay fever sufferers are able to control their hay fever symptoms better and so improve their quality of life, if they are treated by health professionals who have had specific evidence based hay fever training. Or not.

We needed nurses from 15 General Practices to agree to take part. We've sent you this information because one of them is a nurse from your practice. All 15 are helping us find 100 teenagers (age 12 – 18 years) who have hay fever to also take part. If we can't find 100 teenagers then we can't do the research. This sheet explains more about the research and what it means to take part. If you'd like even more information or have any questions which are not covered here, call Vicky Hammersley on 0131 6503234/07969 775912 or you can email her at vicky.hammersley@ed.ac.uk

Why this research is important?

Important research shows that hay fever affects up to 40% of children. Teenagers are particularly affected with symptoms including sneezing, itching and nasal blockage. Lots of teenagers are unable to play sports or concentrate on their schoolwork when their hay fever is bad to the extent that it can impact on their exam performance. We want to see if giving specific hay fever training to nurses and doctors will result in improvements to their teenagers' hay fever – and potentially their exam performance.

Why you are being asked to take part, and what's involved?

We are asking you to take part because you have hay fever and are the right age. We know this because we are working with a nurse from your General Practice who has searched the medical records of all the patients registered there to identify teenagers who have hay fever.

She will be inviting you to attend one special hay fever clinic this summer to discuss your hay fever. We will ask you to fill out one short questionnaire before you go and to fill out one more after you have been. Your clinic appointment should last about 15 minutes, the same amount of time as each questionnaire will take to complete. Taking part therefore requires less than one hour of your time this summer, but it's time that could end up improving the lives of thousands of teenagers with hay fever and potentially improving their exam performance.

What happens next if you decide to take part?

The first thing to do is to fill in the consent form and reply slip and send it back to Vicky Hammersley, the lead researcher on this study. The consent form asks for your permission for us to ask your doctor what medication you have been prescribed or recommended in the past and how often you have visited the practice during previous hay fever seasons. We won't collect or record any medical information not related to your hay fever. The form will also ask your permission to collect your exam data from the Education Authority for one year. Once you have sent the form back to Vicky she'll send you the first questionnaire. The questionnaire asks how your hay fever is affecting your life right then, what symptoms you are having at the time, what medication you are taking to help you and how your hay fever this year compares with previous years.

Next your nurse will invite you to attend her special hay fever clinic once in the summer. Here you'll talk about your hay fever and things you could do to make you feel better and control your symptoms. Half of the nurses taking part will have had their special training before they run their clinic and half will have their training at the end of the study.

Then Vicky will ask you to fill out the questionnaire once more. She'll be able to remind you to do this by texting, emailing or ringing you, whichever you choose. Your involvement starts in March and finishes in September.

Benefits of taking part

As well as this being a unique chance for you to take part in an important research study, we hope you will notice that you are better able to control your hay fever symptoms this summer.

If you don't want to take part

If you don't want to take part you don't have to. You don't need to give a reason and it won't affect the care you get from the health service. If you do decide to take part you are still free to change your mind at any time, also without giving a reason.

What happens to the results of the study?

If you take part we will send you a summary of the results. Since we hope to show a link between specialist training and improved patient health we will also tell doctors about the results to help them with their work. We'll do this by publishing our findings in a report to the Scottish Government's Chief Scientist Office and in medical journals. We expect that the findings will be used in planning future allergy services within the NHS.

Whose study is it?

The Allergy and Respiratory Research Group at Edinburgh University's Centre for Population Health Sciences is undertaking a programme of research with the aim of improving the delivery of care to patients with allergic disorders. This study has been funded by the Scottish Government's Chief Scientist Office and will run until the end of October 2009. It has been approved by the Lothian Research Ethics Committee.

If you need more information or have questions

Please do contact lead researcher Vicky Hammersley who will be pleased to answer any questions about the study, you can contact her on 0131 6503234/07969 775912 or vicky.hammersley@ed.ac.uk

Or you can contact Dr Allison Worth (PhD): Research Fellow, Allergy & Respiratory Research Group, Centre for Population Health Sciences: GP Section, 20 West Richmond Street, The University of Edinburgh, EH8 9DX. Tel: 0131 6509463 or email: allison.worth@ed.ac.uk

Thank you for reading this information. We hope you'll take part in this important research study.

Take a step toward taking part, contact Vicky Hammersley on:

Direct line 0131 6503234

Mobile 07969 775912

Email vicky.hammersley@ed.ac.uk

Or write to her at: Allergy and Respiratory Research Group, Centre for Population Health Sciences:
GP Section, The University of Edinburgh, 20 West Richmond Street, Edinburgh EH8 9DX

General practice information sheet

ADOLESCENT HAYFEVER AND QUALITY OF LIFE

A randomised trial organised by the University of Edinburgh's Allergy and Respiratory Research Group



We would like your assistance with a research study. Please read the following information about why we are doing this research, and what it would involve for the practice. Please ask us if there is anything that is not clear, or if you would like more information.

Why are we doing this research?

Research has shown that hay fever affects up to 40% of children, with adolescents being particularly affected. Common symptoms are sneezing, itching and nasal blockage. Sometimes children find it hard to concentrate on their schoolwork or to play sports when they are suffering from hay fever. We want to see if training nurses and doctors to better help people manage their hay fever will result in improvements in children's hay fever, and potentially their exam performance. If so, this should result in improvements in children's ability to undertake activities and help them to enjoy their lives more during the summer.

What will happen in the study?

This is a randomised controlled trial. We aim to recruit intervention and control practices. The intervention is in two phases, the health care professional (HCP) intervention is a one day short course run by Education for Health (Essential Asthma and Allergic rhinitis). Those HCPs in the intervention arm will be asked to attend this course in Spring 2009. The course is free of charge, and backfill costs will be covered where required. The next phase of the intervention is for HCPs in the intervention and control practices to see patients aged 12-18 years with a history of hay fever in a clinic in early Summer 2009. This will be to discuss their hay fever and ways to better help them to control their symptoms.

Practice staff will be asked to identify eligible children and young adults with hay fever from the medical records, with the help of a search strategy, mail out invitations to those eligible, and send reminders after two weeks. Those children who consent to take part will be required to make a clinic appointment, and the researcher, Vicky Hammersley, will liaise with the practice to ensure these appointments are made. Children who agree to take part in the study will be required to complete three sets of questionnaires; however this will be facilitated by the researcher.

Why has my practice been identified?

We are looking for assistance from practices in the Lothian.

What are the search criteria?

Using Read code clinical terms v2 the following searches will be used to identify eligible patients:

- Patients aged 12-18 years currently registered,
- Patients with a recorded diagnosis of hay fever (H17..),
- and/or evidence of use of hay fever medication: oral antihistamines and topical steroids (c8... and c6...).

What are the exclusion criteria?

Patients will be excluded if they are unable to give consent or are taking part in any other clinical trials involving treatments for allergic rhinitis.

Are any medicines or treatment involved in this study?

We are not testing any new medicines in this study.

What are the possible disadvantages and risks of taking part?

The HCPs in the control practices will not receive the allergy training for the duration of the trial, they will continue to provide the routine clinical care for their

patients. The control practices will be invited to attend the Essential Asthma and Allergic Rhinitis one day course when the trial is complete.

What are the possible benefits of taking part?

It is hoped that there will be improvement in the control of hay fever symptoms in participants as a result of taking part in this study.

What if there is a problem?

Please contact Vicky Hammersley (contact details below) if you have any complaints about this study, and they will be addressed by the research team.

Who is carrying out this study?

The Allergy and Respiratory Research Group at Edinburgh University's Division of Community Health Sciences is undertaking a programme of research with the aim of improving the delivery of care to patients with allergic disorders. This study has been funded the Scottish Government's Chief Scientist Office and will run until the end of October 2009.

What will happen to the results of the study?

We will publish the findings in a report to the Scottish Government's Chief Scientist Office and in medical journals. We expect that the findings will be used in planning future allergy services within the NHS.

What if I have some questions about the study?

Vicky Hammersley will be pleased to answer any questions about the study, you can contact her on 0131 6503234/07969 775912 or vicky.hammersley@ed.ac.uk

Or you can contact Dr Allison Worth (PhD):

Research Fellow, Allergy & Respiratory Research Group, Division of Community Health Sciences: GP Section, The University of Edinburgh. Tel: 0131 6509463 or email: allison.worth@ed.ac.uk

Thank you very much for taking the time to read this information.

Appendix 5: Consent forms

Consent form for 12-15 years

MANAGING YOUR HAY FEVER

A study organised by the University of Edinburgh's Allergy and Respiratory Research Group.



Name (please print) _____ DoB _____

Please initial box

1. I have read and understood the information sheet for the above study and have had the opportunity to ask questions.
2. I understand that it is OK to stop taking part at any time.
3. I understand that the study will involve filling in questionnaires about my hay fever
4. I understand that if the results of the study are published it will not be possible to identify me.
5. I understand that if I do decide to withdraw from the study, the researchers cannot use the information already collected up to that point without my consent.
6. I understand that by giving my preferred telephone number and/or email address to the researchers I am agreeing to be contacted by them.
7. I am happy for Vicky to tell my GP that I am taking part in this study and get information about my hay fever.

8. I am happy for Vicky to obtain my assessment/exam results from the Education Authority.

9. I agree to take part in this study.

Signature

Date

Please return this signed consent form to Vicky Hammersley in the envelope provided.

Thank you for helping us with this study

Consent form for 16-18 years

MANAGING YOUR HAY FEVER

A study organised by the University of Edinburgh's Allergy and Respiratory Research Group



Name (please print) _____ DoB _____

Delete as appropriate

I confirm that I have read and understand the information leaflet for the above study

Yes/No

I understand that if I have any questions about the study I can contact Vicky

Yes/No

I understand that the study will involve filling in questionnaires about my hay fever

Yes/No

I understand that all the information about me recorded for this project will be completely anonymous. If the results of the study are published it will not be possible to identify me.

Yes/No

I understand that it is up to me whether I take part, and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected

Yes/No

I understand that if I do decide to withdraw from the study, the researchers cannot use the information already collected up to that point without my consent.

Yes/No

I understand that by giving my preferred telephone number and email address to the researchers I am agreeing to be contacted by them.

Yes/No

I am happy for the Vicky to tell my GP that I am taking part in this study and get information about my hay fever.

Yes/No

I am happy for Vicky to obtain my assessment/exam results from the Education Authority.

Yes/No

I agree to take part in the above study.

Signature

Date

Please return this signed consent form to Vicky Hammersley in the envelope provided.

Thank you for helping us with this study.

Consent form for practices

ADOLESCENT HAYFEVER AND QUALITY OF LIFE

A randomised trial organised by the University of Edinburgh's Allergy and Respiratory Research Group



Once you have read the information sheet provided please answer the following questions.

Delete as appropriate

We have read and understood the information provided.	Yes/No
Our practice is willing to take part in this study.	Yes/No
We are happy for Vicky Hammersley to contact our practice manager.	Yes/No

Please sign and date this form and return it to Vicky Hammersley in the envelope provided:

Practice Manager Name

Signature of practice representative

Date

Appendix 6: Patient data collection form

Please ask your parents/guardians to help you complete these questions

Date today: / /

1. Please give your full name	
2. Please give you date of birth	
3. Are you male or female?	
4. What year are you in at school?	
5. What was your last school exam/assessment?	
6. What is your next school exam/assessment?	
7. How old were you when you first got hayfever?	
8. Which month of the year do your symptoms start?	
9. What medicines do you usually get from your doctor?	
10. What medicines do you usually buy from the chemist?	
11. Do you have regular access to the internet?	
12. Please list your contact details and tick which way you would prefer to be contacted by Vicky.	Mobile phone:
	Home phone:

	Email address:
	Home address:

Appendix 7: Description of the derivation of the two different Indices of Multiple Deprivation across English and Scottish sites

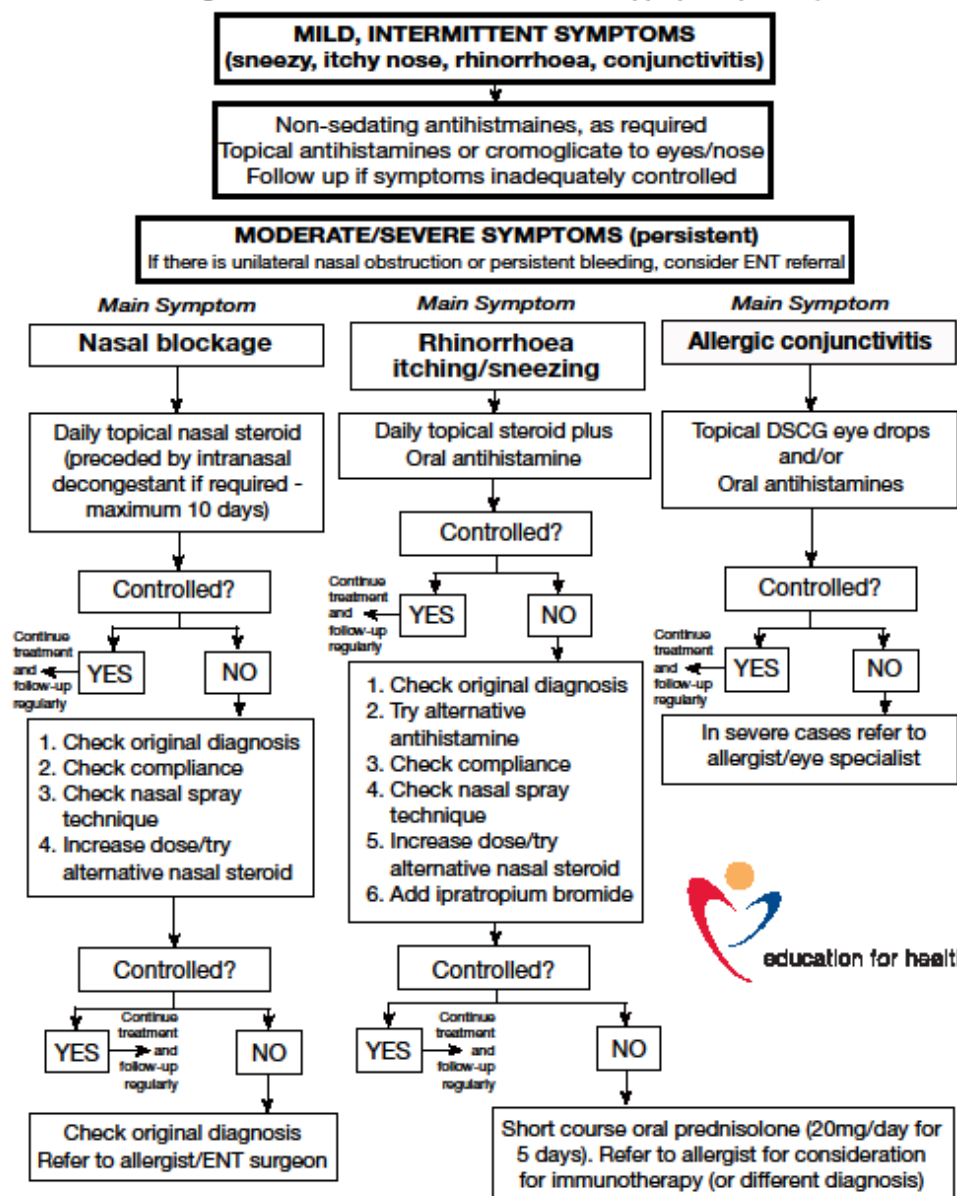
The Index of Multiple Deprivation 2004(Noble et al. 2004) (IMD 2004) is a measure of multiple deprivation at a small level and is based on dimensions of deprivation which can be measured separately. The IMD 2004 contains seven domains of deprivation: income, employment, health and disability, skills and training, barriers to housing and services, living environment and crime. The IMD 2004 score was obtained for each cluster (general practice) by using linked files which first associated each cluster's complete post code with a Super Output Area (SOA) and then the SOA with the IMD. General practice IMD 2004 scores for the practices in England were used as a proxy measure for the population of patients registered, as patient level IMD 2004 scores were not available.

The Scottish Index of Multiple Deprivation(The Scottish Government 2006) (SIMD) is the Scottish Government's official measure for identifying areas of deprivation in Scotland and is based on 37 indicators across seven domains: current income, employment, health, education, housing, geographic access to services, and crime. Different areas of Scotland are assigned to one of five quintiles according to their SIMD score, quintiles are ranked by deprivation with Quintile 1 containing the 20% most deprived datazones in Scotland and Quintile 5 containing the 20% least deprived datazones in Scotland. The weighted mean of quintiles 1-5 was calculated for each cluster based on the number of patients matched to each quintile for the general practices in Lothian and Borders and this mean quintile score was used for the minimization.

Appendix 8: British Society of Allergy and Clinical Immunology Guidelines

MANAGEMENT OF HAYFEVER/PERENNIAL ALLERGIC RHINITIS

(Diagnosis should be based on the history and results of skin prick tests/sIgE's
Allergen avoidance should be recommended in appropriate patients)



N.B. DEPOT CORTICOSTEROIDS ARE NO LONGER RECOMMENDED FOR TREATMENT OF HAYFEVER

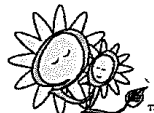
© Education for Health 2006

Appendix 9: Standardised Rhinoconjunctivitis Quality of Life Questionnaire

RHINOCONJUNCTIVITIS QUALITY OF LIFE QUESTIONNAIRE WITH STANDARDISED ACTIVITIES (RQLQ(S))

SELF-ADMINISTERED UNITED KINGDOM VERSION (≥12 years)

© 1997
QOL TECHNOLOGIES Ltd.



For further information:

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Professor
20 Marcuse Fields
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PO18 8NA, England
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Fax: +44 1243 573680
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Web: <http://www.qoltech.co.uk>

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NOVEMBER 2008

RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
UNITED KINGDOM VERSION
SELF-ADMINISTERED ≥ 12

PATIENT ID _____

DATE _____

Page 1 of 4

Please complete **all** questions by circling the number that best describes how **troubled** you have been during the **last week as a result of your nose/eye symptoms**.

ACTIVITIES

How **troubled** have you been by each of these activities during the **last week** as a result of your nose/eye symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
1. REGULAR ACTIVITIES AT HOME AND AT WORK/ SCHOOL (tasks that you have to do regularly at work/school and around your home)	0	1	2	3	4	5	6
2. SOCIAL ACTIVITIES (e.g., activities with your family and friends, playing with children and pets, sex, hobbies)	0	1	2	3	4	5	6
3. OUTDOORS ACTIVITIES (e.g., gardening, mowing the lawn, sitting outdoors, sports, going for a walk)	0	1	2	3	4	5	6

SLEEP

How **troubled** have you been by each of these sleep problems during the **last week** as a result of your nose/eye symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
4. Difficulty getting to sleep	0	1	2	3	4	5	6
5. Wake up during night	0	1	2	3	4	5	6
6. Lack of a good night's sleep	0	1	2	3	4	5	6

C:\Documents and Settings\Jilly\My Documents\WordPerfect\Wpdocs\QotqRhinocont12 +1SRQLQS + 12 UK ENGLISH.DOC

RHINOCONJUNCTIVITIS
 QUALITY OF LIFE QUESTIONNAIRE (S)
 UNITED KINGDOM VERSION
 SELF-ADMINISTERED ≥ 12

PATIENT ID _____

DATE _____

Page 2 of 4

NON-NOSE/EYE SYMPTOMS

How **troubled** have you been during the **last week** as a result of these symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
7. Fatigue	0	1	2	3	4	5	6
8. Thirst	0	1	2	3	4	5	6
9. Reduced productivity	0	1	2	3	4	5	6
10. Tiredness	0	1	2	3	4	5	6
11. Poor concentration	0	1	2	3	4	5	6
12. Headache	0	1	2	3	4	5	6
13. Worn out	0	1	2	3	4	5	6

PRACTICAL PROBLEMS

How **troubled** have you been by each of these problems during the **last week** as a result of your nose/eye symptoms?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
14. Inconvenience of having to carry tissues or handkerchief	0	1	2	3	4	5	6
15. Need to rub nose/eyes	0	1	2	3	4	5	6
16. Need to blow nose repeatedly	0	1	2	3	4	5	6

RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
UNITED KINGDOM VERSION
SELF-ADMINISTERED ≥ 12

PATIENT ID _____

DATE _____

Page 3 of 4

NASAL SYMPTOMS

How **troubled** have you been by each of these symptoms during the **last week**?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
17. Stuffy/blocked	0	1	2	3	4	5	6
18. Runny	0	1	2	3	4	5	6
19. Sneezing	0	1	2	3	4	5	6
20. Catarrh (drainage of mucous down the back of your nose)	0	1	2	3	4	5	6

EYE SYMPTOMS

How **troubled** have you been by each of these symptoms during the **last week**?

	Not troubled	Hardly troubled at all	Somewhat troubled	Moderately troubled	Quite a bit troubled	Very troubled	Extremely troubled
21. Itchy eyes	0	1	2	3	4	5	6
22. Watery eyes	0	1	2	3	4	5	6
23. Sore eyes	0	1	2	3	4	5	6
24. Swollen eyes	0	1	2	3	4	5	6

RHINOCONJUNCTIVITIS
QUALITY OF LIFE QUESTIONNAIRE (S)
UNITED KINGDOM VERSION
SELF-ADMINISTERED ≥ 12

PATIENT ID _____

DATE _____

Page 4 of 4

EMOTIONAL

How often during the **last week** have you been troubled by these emotions as a result of your nose/eye symptoms?

	None of the time	Hardly any time at all	A small part of the time	Some of the time	A good part of the time	Most of the time	All of the time
25. Frustrated	0	1	2	3	4	5	6
26. Impatient or restless	0	1	2	3	4	5	6
27. Irritable	0	1	2	3	4	5	6
28. Embarrassed by your symptoms	0	1	2	3	4	5	6

Appendix 10: Visual Analogue Scale


Managing your hay fever study: Symptom Score questionnaire

Name

Study Number

Date

“How has your hay fever been this week?”

No symptoms 😊  ☹️ Very bad symptoms

PLEASE MARK A POINT IN THE LINE ABOVE

Appendix 11: Description of extension to the second year of recruitment

The protocol for this trial stated a recruitment period of one year, relating to one hay fever season, however despite recruiting enough adolescents into the trial, the number of complete primary outcome data sets was not enough to achieve the required power. The power calculation in the protocol was based on requiring 80% power to detect as significant at the 5% level a mean intervention effect of 0.5 on the RQLQ scale, assuming a standard deviation of 1.2. This gave an unadjusted sample size of 180, which inflated to 220 assuming an ICC of 0.02 and a mean cluster size of 10 (i.e. a design effect of 1.22, giving 22 clusters of size 10). At the end of data collection, final RQLQ(S) data were collected from 180 patients in 23 clusters, however only 156 patients in 21 clusters returned both baseline and final RQLQ(S). The implications of this loss of follow-up data on the power of the study are shown in the table below.

Table: Power calculations for varying ICCs to detect the required effect size of 0.5

ICC	No. required to detect effect size of 0.5	Effect size detectable with existing nos. with 80% power	Power for 0.5 effect size with existing nos.
0.01	201	0.53	0.76
0.02	220	0.55	0.72
0.03	238	0.58	0.68

The table shows that based on 180 subjects with a final RQLQ(S) and an ICC of 0.02 (the original estimate) the power is reduced to 72%, or that we required 220 patients to detect the required effect size. This coincidentally is the same as the original estimate, but the loss of power due the variation in cluster size from the 21 clusters is offset by a reduction in the design effect from having more clusters with fewer subjects in them (Eldridge, Ashby et al. 2006).

Appendix 12: Terms of reference for Trial Steering Committee

TRIAL STEERING COMMITTEE (TSC)

Cluster randomised controlled trial of an educational intervention for healthcare professionals for the management of school-age children with hay fever.

TERMS OF REFERENCE

- Overall supervision of the trial
- Approval of the final version of the protocol
- Assuring patient safety and ethics
- Monitoring progress of the research to its overall objectives
- Monitoring adherence to the protocol
- Approving changes to the protocol
- Monitoring the progress of the trial
- Considering any new information that might be relevant to the trial and its continuation
- Monitoring the dissemination of results
- Handling complaints from participants if these have not been resolved locally

MEMBERSHIP AND AFFILIATION OF THE TSC

Chair:

Professor Tony Avery, Professor in Primary Care, School of Community Health Sciences, University of Nottingham.

Independent Members:

Dr Sarah Rodgers, Lecturer in Pharmacy, School of Pharmacy, University of Nottingham.

Dr Glenis Scadding, Consultant Physician in Allergy and Rhinology, Royal National Throat, Nose and Ear Hospital, London.

Dr Sarah Armstrong, Senior Lecturer in Medical Statistics, School of Community Health Sciences, University of Nottingham.

Project Team

Victoria Hammersley, CSO Research Fellow/PhD student, Division of Community Health Sciences, University of Edinburgh.

Professor Aziz Sheikh, Professor of Primary Care Research & Development
Division of Community Health Sciences, University of Edinburgh.

Dr Samantha Walker, Director of Research, Education for Health, Warwick & Senior Lecturer (hon.), University of Edinburgh.

Dr Rob Elton, Consultant Statistician, University of Edinburgh.

Appendix 13: Consort Checklist

PAPER SECTION and topic	Item	Descriptor	Reported on Page No.
TITLE & ABSTRACT	1*	How participants were allocated to interventions (e.g., “random allocation”, “randomised”, or “randomly assigned”), <i>specifying that allocation was based on clusters</i>	iii
INTRODUCTION Background	2*	Scientific background and explanation of rationale, <i>including the rationale for using a cluster design</i> .	44
METHODS Participants	3*	Eligibility criteria for participants <i>and clusters</i> and the settings and locations where the data were collected.	58-63
Interventions	4*	Precise details of the interventions intended for each group, <i>whether they pertain to the individual level, the cluster level or both</i> , and how and when they were actually administered.	65-69
Objectives	5*	Specific objectives and hypotheses, <i>and whether they pertain to the individual level, the cluster level or both</i> .	47
Outcomes	6*	Report clearly defined primary and secondary outcome measures, <i>whether they pertain to the individual level, the cluster level or both</i> , and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	70
Sample size	7*	How <i>total</i> sample size was determined (<i>including method of calculation, number of clusters, cluster size, a coefficient of intracluster correlation (ICC or k), and an indication of its uncertainty</i>) and, when applicable, explanation of any interim analyses and stopping rules.	64
Randomisation. Sequence generation	8*	Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification, <i>matching</i>).	63
Allocation concealment	9*	Method used to implement the random allocation sequence, <i>specifying that allocation was based on clusters rather than individuals</i> and clarifying whether the sequence was concealed until interventions were assigned.	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (Masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	63
Statistical methods	12*	Statistical methods used to compare groups for primary outcome(s) <i>indicating how clustering was taken into account</i> ; methods for additional analyses, such as subgroup analyses and adjusted analyses.	74
RESULTS Participant flow	13*	Flow of <i>clusters and</i> individual participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of <i>clusters and</i> participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	80
Recruitment	14	Dates defining the periods of recruitment and follow-up.	71
Baseline data	15*	Baseline information for each group <i>for the individual and cluster levels as applicable</i>	77
Numbers analyzed	16*	Number of <i>clusters and</i> participants (denominator) in each group included in each analysis and whether the analysis was by “intention-to-treat”. State the results in absolute numbers when	79

		feasible (e.g., 10/20, not 50%).	
Outcomes and Estimation	17*	For each primary and secondary outcome, a summary of results for each group measures <i>for the individual or cluster level as applicable</i> , and the estimated effect size and its precision (e.g., 95% confidence interval) <i>and a coefficient of intracluster correlation (ICC or k) for each primary outcome</i> .	84
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	89
Adverse events	19	All important adverse events or side effects in each intervention group.	n/a
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	100
Generalisability	21*	Generalisability (external validity) <i>to individuals and/or clusters (as relevant)</i> of the trial findings.	115
Overall evidence	22	General interpretation of the results in the context of current evidence.	115

Appendix 14: Published papers

Trial protocol

Hammersley et al. *Trials* 2010, **11**:84
<http://www.trialsjournal.com/content/11/1/84>



STUDY PROTOCOL

Open Access

Protocol for the adolescent hayfever trial: cluster randomised controlled trial of an educational intervention for healthcare professionals for the management of school-age children with hayfever

Victoria S Hammersley^{1*}, Samantha Walker², Rob Elton¹, Aziz Sheikh¹

Abstract

Background: Seasonal allergic rhinitis (hayfever) is common and can contribute to a considerable reduction in the quality of life of adolescents. This study aims to examine the effectiveness of standardised allergy training for healthcare professionals in improving disease-specific quality of life in adolescents with hayfever.

Methods/Design: Adolescents with a history of hayfever registered in general practices in Scotland and England were invited to participate in a cluster randomised controlled trial. The unit of randomisation is general practices. The educational intervention for healthcare professionals consists of a short standardised educational course, which focuses on the management of allergic rhinitis. Patients in the intervention arm of this cluster randomised controlled trial will have a clinic appointment with their healthcare professional who has attended the training course. Patients in the control arm will have a clinic appointment with their healthcare professional and will receive usual care.

The primary outcome measure is the change in the Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities (RQLQ(S)) score between baseline and six weeks post-intervention in the patient intervention and control groups.

Secondary outcome measures relate to healthcare professionals' understanding and confidence in managing allergic rhinitis, changes in clinical practice, numbers of consultations for hayfever and adolescent exam performance. A minimum of 11 practices in each arm of the trial (10 patients per cluster) will provide at least 80% power to demonstrate a minimal clinically important difference of 0.5 in RQLQ(S) score at a significance level of 5% based on an Intraclass Correlation Coefficient (ICC) of 0.02.

Discussion: At the time of submission, 24 general practices have been recruited (12 in each arm of the trial) and the interventions have been delivered. Follow-up data collection is complete. 230 children consented to take part in the trial; however complete primary outcome data are only available for 160. Further recruitment of general practices and patients will therefore take place in the summer of 2010.

Trial Registration: Current Controlled Trials ISRCTN95538067

* Correspondence: vicky.hammersley@ed.ac.uk

¹Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Medical School, Teviot Place, Edinburgh, EH8 9AG, UK



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Background

In the UK, allergic diseases have an overall lifetime prevalence of about 30% in the general population, with a considerably higher prevalence in young people [1,2]. Intermittent allergic rhinitis (also known as seasonal allergic rhinitis or hayfever) affects up to 30% of adults and 40% of children at some time in their lives [2-5]. Up to 80% of patients with asthma also have allergic rhinitis, and nearly 40% of those with allergic rhinitis have co-existing asthma [6,7]. Allergic rhinitis and its major co-morbidity asthma cause significant health burdens to the individual, and the impairment of quality of life experienced by patients with rhinitis is at least as severe as that of patients with asthma [8]. A recent editorial in *The Lancet* reported that the economic burden posed by allergic rhinitis has almost doubled since 2000 [9].

The Allergic Rhinitis in Asthma (ARIA) classification scheme was introduced in 2001 and reinforced in 2008; this subdivides allergic rhinitis into "intermittent" or "persistent" disease [8,10]. Previously, allergic rhinitis was subdivided based on time of exposure into "seasonal" (more commonly known as hayfever), "perennial" and "occupational" forms. Intermittent allergic rhinitis (IAR) is defined as symptoms being present for less than four days per week for less than four weeks and persistent allergic rhinitis refers to symptoms that are present for more than four days a week and for more than four weeks. This new ARIA classification has not yet been widely adopted in UK primary care, and patients with IAR are thus still given a Read code [11] for seasonal allergic rhinitis in their medical records and hence these terms and codes need to be searched when identifying local populations.

Common symptoms of allergic rhinitis include sneezing, itching, watery rhinorrhoea and nasal blockage, and these can have a considerable negative impact on children in terms of their physical, social and psychological well-being, and academic performance. Research has, for example, shown that children with allergic rhinitis indicated that they experienced particular problems with their schoolwork [12], and a recent case control study of teenage hayfever sufferers showed an association with an increased risk of unexpectedly dropping a grade in summer examinations (adjusted odds ratio 1.43; 95% CI 1.13-1.81) [13]. Children may also lose sleep, have reduced ability to concentrate, and have a risk of developing a major depressive disorder [14]. The achievement of optimal outcomes in children with allergic rhinitis depends on timely diagnosis, followed by implementation of measures to reduce allergen exposure, selection of safe and effective treatments and patient adherence to therapeutic regimens. This can be facilitated by appropriate training of healthcare professionals (HCPs)

and patients in the optimum treatment choices, timing of medication commencement, appropriate techniques to ensure appropriate delivery of intranasal treatments and ensuring that compliance remains optimal.

Treatments for allergic rhinitis aim to minimise or eliminate symptoms, optimise quality of life and reduce the risk of developing co-morbidities. A report published in 2003 *Allergy - the unmet need*, commissioned by the Royal College of Physicians, clearly demonstrated current deficiencies in allergy services in the UK, and made a number of proposals to improve patient care, both in primary and secondary care. These findings have been confirmed in relation to allergic rhinitis in a UK survey of general practitioners whose practice had a self-declared interest in the management of allergic and respiratory disorders [15], which found considerable variation in their awareness and management of allergic rhinitis. This again suggests that an educational intervention covering all aspects of management of allergic rhinitis in primary care is both timely and important.

The House of Lords Science and Technology Committee report on Allergy (2006-7) recommended that the Department for Children, Families and Schools should review the clinical care that children receive at school, and should reassess the way they are supported through the examination season [16]. However, the knowledge and training in allergic diseases of teachers and support staff may not be sufficient to support children through this period. Enhancing the role of primary care professionals in ensuring control of allergy symptoms by improving training and engaging the patient in self-care may be a more beneficial and safer approach.

A multi-centre community based randomised controlled trial showed that standardised allergy education given to HCPs improved disease-specific quality of life in patients with perennial rhinitis [17]. This study found that a structured educational intervention was feasible to deliver in primary care, was well received by GPs and nurses, and improved outcomes in adults with perennial rhinitis. The present trial is building on this by testing the effectiveness of a modified version of this educational intervention in adolescents with hayfever.

Aims of the study

The primary aim of this study is to examine the effectiveness of standardised allergy training in increasing disease-specific quality of life of adolescents with hayfever. A customised one-day short course, which focuses on allergic rhinitis and its main co-morbidity asthma, will be delivered to health care professionals.

The secondary aims are to examine whether attending an allergic rhinitis and asthma short course can enhance knowledge and skills of practitioners who consult with

hayfever sufferers, changes in clinical practice, numbers of consultation for hayfever and adolescent exam performance.

Specific objectives

1. To evaluate the effectiveness of standardised allergy training for HCPs on adolescent (12-18 years) rhinitis-specific quality of life.
2. To examine the impact of improving symptoms of hayfever on examination performance of adolescents.
3. To assess the change in allergy practice, improvement in confidence and understanding, and management of allergy symptoms of trained healthcare professionals.

Methods/Design

Trial design

We are conducting a pragmatic cluster randomised trial. Trial practices will receive either i) allergic rhinitis and asthma management training with support materials (rhinitis management algorithm and leaflet) or ii) support materials alone.

Eligibility of general practices for entering the trial

Inclusion criteria

- General practices within the recruitment areas of the Scottish Primary Care Research Network (SPCRN) and the Northern and Yorkshire Research Network (NYREN).
- Practices that agreed to participate in the study and were willing to allow healthcare professionals to attend a one-day short course on allergic rhinitis and asthma.

Exclusion criteria

- Practices not interested in participating and/or unable to release practice staff to attend the training.

Eligibility of patients for entering the trial

All young people aged 12-18 years with hayfever were eligible to participate. Hayfever was defined by the presence of a documented clinician diagnosis in the patient's health record and any evidence of treatment used for allergic rhinitis. Patients were excluded if they were unable to give consent or were taking part in any other clinical trials involving treatments for allergic rhinitis.

Recruitment

General practices and health care professionals

We applied to SPCRN and NYREN for their assistance with practice recruitment. They wrote to general practices informing them of the study with an information flyer. Additional contact was made with general practices in Scotland via NHS Education for Scotland (NES)

and local informal contacts. Where practices expressed an interest in participating, an information sheet was sent to each practice with the offer of a face-to-face or telephone discussion at which the study was explained in more details. A member of the practice team (Lead GP or Practice Manager) then signed a consent form if the practice decided to participate. Practices were asked to nominate a member of their team who regularly sees patients with hayfever, but who has not previously received postgraduate allergy training. Twenty four general practices were recruited.

Patient recruitment

In order to avoid the risk of allocation bias, practices were asked to identify all eligible patients aged 12-18 years, through searches of the practice electronic medical record, prior to randomisation. Patients with a recorded diagnosis of hayfever (Read code clinical terms v2: H17), and/or evidence of use of hayfever medication (oral antihistamines and topical steroids, drugs used in nasal allergy and topical nasal decongestants; Read code clinical terms v2: c8, c6, 18 and 19) were eligible to participate. The practices were asked to write to eligible participants sending an invitation letter with a participant information sheet, consent form and patient data collection form for return directly to the study team. Two versions of the consent form were used, one for 12-15 year old participants, which included a space for parental/guardian consent, and one for 16-18 year old participants. All recruitment materials were approved by Lothian 2 Research Ethics Committee. Reminder invitations were sent to non-responders by the practice nurse two weeks after the initial mailing. Consenting patients were asked to express their preferred method of communication with the research team: email, text messages or post.

Intervention

The intervention was in two phases: the first phase was at the level of the practice/HCP and the second at the level of the patient.

HCP training

Those practices randomly allocated to the intervention arm were invited to nominate a HCP to attend an allergic rhinitis and asthma short course run by Education for Health. The short course was delivered by Education for Health trainers; the programme for this course is available in Additional file 1. Those practices randomised to the control arm received written information.

Appointment with HCP (patients in both groups)

Once a patient had consented to take part in the trial by returning the signed consent and data collection forms, they were invited by email, text message or phone to make an appointment with the nominated HCP by the research team. The research team liaised with the

general practice to ensure all consenting patients had made an appointment during May-June 2009/10. Patients were seen by the HCP in their usual clinic setting. No guidance was given to either group about the format of the consultation.

Allocation of trial interventions

The general practice was the unit of allocation. Randomisation to intervention or control was carried out separately within each of the five participating regions: Lothian; Borders; Durham and Tees Valley; Northumberland Tyne and Wear, York. For the four regions with more than two practices, this was done using minimisation based on achieving optimum balance for practice list size (three strata <5000, >5001, but <10000, >10000 patients currently registered) and deprivation score (Index of Multiple Deprivation), according to the methods described by Carter and Hood [18].

The reason for randomisation by centre was to help ensure an even distribution of intervention and control practices as there is likely to be a geographical variation in pollen counts between centres.

Outcome measures

Primary outcome

- The change in the RQLQ(S) score between baseline and 6 weeks post-intervention in the intervention and control groups.

The RQLQ(S) measures the problems experienced by young people with hayfever. This is a validated and widely used tool in clinical trials [12,17,19,20]. It has been designed to ask patients about seven domains: activity; sleep; non-nose/eye symptoms; practical problems; nasal symptoms; eye symptoms; and emotional function.

Quality of life using the validated RQLQ(S) was measured at the beginning of the hayfever season (March 2009) prior to the HCP clinic appointment, and repeated at six weeks post-intervention.

Secondary outcomes

- Weekly pollen count data collected over the duration of trial.

Clinical outcomes

- Patient reported symptom scores using a visual analogue scale.
- Overall assessment of hayfever symptoms compared with the previous season.
- Number of general practitioner and practice nurse consultations for hayfever, prescribed (from clinical records) and over-the-counter (from patients) medication data were collected.

Educational outcomes

Educational data will be collected via the Local Education Authority. This will be based on final grades for the age-specific assessment adjusted for pre-trial grades, where possible.

Process outcomes: assessment of change in clinical practice

These were measured using a questionnaire assessing change in allergy practice and improvement in confidence, understanding and management of allergic symptoms. All HCPs in the intervention arm were asked to complete this questionnaire immediately before and after the training, and after seeing their last patient in the trial.

Sample size

There is little published literature about the likely design effect size in healthcare interventions and hayfever quality of life, however using data from a previous parallel group study using the RQLQ in adults with perennial rhinitis [17], a mixed-model analysis of variance gave an F-ratio of less than unity, indicating that there was less variation between practices than would be expected by chance (data available on request). This means that the inter-practice variance and hence the ICC is estimated as zero, and there would thus be no anticipated design effect for the proposed cluster randomised trial. There are however obvious differences between the study in adults and this cluster trial in adolescents, including the trial design; estimates of the between-practice variation in the proposed study and its effect on sample size are shown in Table 1.

Samsize [21] was used for sample size calculations. A cluster size of 10 was chosen as pilot work suggested that it should be possible to recruit at least this number of adolescents with diagnosed current hayfever from most general practices (data available on request).

Taking account of the cluster design, using a standard deviation of 1.2 [20] with a power of 80% to detect a minimal clinically important difference of 0.5 in RQLQ (S) score at a significance level of 5%, an estimate of the cluster size of 10 and an ICC of 0.02 required a total of 22 clusters and an adjusted sample size of 220 patients (unadjusted 180).

Based on these figures, we aimed to recruit at least 22 practices, inflated by 20% to account for possible

Table 1 Number of patients needed with varying ICCs

ICC	Cluster size	No. of clusters	No. of patients
0.01	10	20	200
0.02	10	22	220
0.05	10	24	240

losses to follow-up, resulting in 22 clusters (practices) recruiting 12 patients per practice, giving a total of 264 patients in the study (i.e. 132 per arm).

With these numbers, the study is sufficiently powered for the primary outcome measure; it is however likely to be underpowered for the secondary educational outcomes based on examination data [13].

Compliance

All practices were given clear written information on what the study involved and were visited by the researcher prior to agreeing to take part in the study. In order to maximise the opportunities for intervention HCPs to attend the training, the course was run twice on separate dates in two different venues; all intervention HCPs attended a training day. The researcher assisted the practice with the mailings and reminders to eligible patients, and a clear account of payment for all practice time was given to the practices at the beginning, which included administrative time and backfill for the HCPs attending the training. The control group practices were offered the same short course at the end of the study and this was attended by nine out of the 12 control practices.

Withdrawal of patients from the study

There were three points at which consenting patients could withdraw from the study:

- i) prior to completing baseline questionnaires
- ii) prior to attending the practice nurse appointment
- iii) prior to completing the six weeks post-intervention questionnaires.

Statistical analysis

Data analysis, using the following analysis plan, will be undertaken blind to the allocation arm. The primary analysis will be a per protocol analysis on complete cases only. An intention-to-treat analysis using the last observation carried forward is not feasible since imputing of the baseline data (which were collected before the pollen season) for subjects whose final RQLQ(S) is missing would not be a conservative assumption. This is because the lack of change from a value measured before the hayfever season might be better than expected. (i.e. baseline values may be low on a scale of 0-6 where 0 is not troubled and 6 is extremely troubled, and imputing these data for an RQLQ measured at the peak of the season, which may have been high might result in over-estimation of the intervention effect if more cases had missing data in the intervention group.)

Descriptive analyses

Describing baseline characteristics of patients and practices
a) For each treatment arm, we will describe:

- i) Patient age (mean and SD) and sex (number and percentage)
- ii) Practice list size (median and IQR, or mean and SD if normally distributed)
- iii) Practice population by age group (number and percentage)
- iv) Practice deprivation (IMD or proxy measure)
- v) Whole time equivalent GPs and practice nurses per practice (median and IQR, or mean and SD if normally distributed).

Comparison between treatment arms

The difference in the validated RQLQ(S) score between the intervention and control groups at baseline and six weeks post-intervention will be compared.

Adjusting for

1. Practice level stratum (region, list size and IMD or proxy) and baseline RQLQ(S).
2. Practice level stratum (region, list size and IMD or proxy). This will potentially be a more powerful comparison in the event that substantial numbers of subjects provide follow-up data, but not baseline data.

Multi-level modelling using a random-effects model will be used to take account of between and within cluster variation, adjusting for strata and individual covariates for example pre-intervention level of RQLQ(S). Estimates and standard errors of the intervention effects will be reported and normal chi-square tests on the ratio of these estimates to their standard errors will be used. An estimate and confidence intervals for the ICC will be calculated, adjusting for baseline RQLQ(S). Analysis will be undertaken using MLwiN.

Missing data

RQLQ(S)

The RQLQ(S) is divided into seven domains, with varying numbers of questions per domain, and the overall RQLQ(S) score is calculated from the mean of each domain. Where responses to a whole domain within the RQLQ(S) are missing, this patient will be excluded from the analysis.

Reporting and dissemination

Reporting will adhere to revised CONSORT criteria for cluster trials [22,23].

Trial Steering Committee

The Trial Steering Committee (TSC) will monitor and supervise the trial and comment on any proposed amendments to the protocol. The TSC is chaired by Professor Anthony Avery and Dr Glenis Scadding, Dr Sarah Rodgers and Dr Sarah Armstrong are the other

external members of the committee. The TSC has agreed to operate within the framework suggested in the MRC Guidelines for good clinical practice in clinical trials [24].

Ethical considerations

The clinical trial will be conducted according to the Helsinki Declaration [25], Good Clinical Practice Guidelines [24] and NHS research governance requirements. Patients who have agreed to allow the study team to access their clinical and educational records have provided written informed consent. All patients were made aware that that can withdraw from the research at any time. The study has been approved by Lothian 2 Research Ethics Committee (Reference 08/S1102/37). All appropriate NHS Research and Development approvals have been obtained.

Study timeline

Trial Start: 1 August 2008

Baseline data collection: March 2009 and 2010

Interventions in general practice: April 2009 and 2010 (training), May/June 2009 and 2010 (patient appointments with HCPs)

End of interventions in general practice: June 2009 and 2010

End of 6 week follow-up: August 2009 and 2010

Start of data analysis: September 2010

Planned study end date: December 2010

Duration: 29 months

Current study status

At the time of submission, outcome data has only been obtained for 160 patients from 24 general practices, leading to lower power than was originally intended for the study, and further recruitment is therefore planned in the summer of 2010. It is planned to recruit a further 10 practices, which will achieve the original target of 220 patients if cluster sizes are similar to those for 2009. We calculate that this will give similar power to that originally planned, because the gain in power from having more clusters of smaller size will be counterbalanced by some loss of power from the fact that there was substantial variation in the sizes of the different clusters.

Additional material

Additional file 1: Programme for the Essential Asthma and Allergic Rhinitis Short Course.

Abbreviations

ARIA: Allergic Rhinitis in Asthma; GP: General practice; HCP: health care professional; IAR: Intermittent allergic rhinitis; ICC: Intraclass correlation coefficient; NYREN: Northern and Yorkshire Research Network; RQLQ(S):

Rhinoconjunctivitis Quality of Life Questionnaire with Standardised Activities; SAR: Seasonal allergic rhinitis; SPCRN: Scottish Primary Care Research Network.

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Authors' contributions

AS, VH and SW conceived the study and together led the bid to secure funding for this work and manage the project. RE provided statistical and methodological advice in designing the study and all authors contributed to its implementation. VH was the researcher employed on this project and led the drafting of this paper. VH and AS are guarantors. All authors commented on draft versions, and read and approved the final manuscript.

Competing interests

AS is a research advisor to Education for Health, SW is Director of Education & Research at Education for Health. All other authors declare no competing interests.

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ARTICLE OPEN

Adolescent seasonal allergic rhinitis and the impact of health-care professional training: cluster randomised controlled trial of a complex intervention in primary care

Victoria S Hammersley¹, Rob A Elton¹, Samantha Walker¹, Christian H Hansen² and Aziz Sheikh^{1,3}**BACKGROUND:** Seasonal allergic rhinitis is typically poorly managed, particularly in adolescents, in whom it is responsible for considerable morbidity. Our previous work has demonstrated that if poorly controlled this can impair educational performance.**AIM:** The primary aim of this trial was to assess the impact of a primary care-based professional training intervention on clinical outcomes in adolescents with seasonal allergic rhinitis.**METHODS:** Cluster trial in which UK general practice staff were randomised to a short, intensive workshop on the evidence-based management of seasonal allergic rhinitis. The primary outcome measure was the change in the validated Rhinoconjunctivitis Quality of Life Questionnaire with Standardized Activities (RQLQ(S)) score between baseline and 6 weeks post intervention (minimal clinically important difference = 0.5). Secondary outcome measures of interest included health-care professionals' knowledge and confidence in managing seasonal allergic rhinitis, number of seasonal allergic rhinitis-related consultations, relevant treatments prescribed and symptom scores.**RESULTS:** Thirty-eight general practices were randomised (20 in the intervention arm) and 246 patients (50.2% males, mean age 15 years) were included in the primary outcome analysis. Health-care professionals' knowledge and confidence of the clinical management of seasonal allergic rhinitis improved. This did not, however, result in clinically or statistically significant improvements in RQLQ(S): -0.15, (95% confidence interval, -0.5 to +0.2). There were no differences in consultation frequency, treatments issued for seasonal allergic rhinitis or symptom scores.**CONCLUSIONS:** Although associated with increases in professionals' self-assessed confidence and understanding of seasonal allergic rhinitis management, this intensive training workshop did not translate into improvements in adolescents' disease-specific quality of life or a reduction in rhinitis symptoms.

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INTRODUCTION

Seasonal allergic rhinitis (also known as intermittent allergic rhinitis) is a very common condition in adolescence, with national¹ and international²⁻⁴ studies suggesting that up to 40% of young people may be affected. It can be responsible for considerable morbidity in its own right; research focusing on children and adolescents with seasonal allergic rhinitis has identified particular problems with schoolwork,⁵ exam performance⁶ as well as loss of sleep and reduced ability to concentrate.^{7,8} As a consequence, seasonal allergic rhinitis poses a substantial and increasing economic burden on health-care systems and the society at large.⁹ American estimates have, for example, suggested that health-care expenditure associated with allergic rhinitis has doubled since 2000, increasing to more than \$11 billion.¹⁰ It is now better recognised that many people with seasonal allergic rhinitis also have coexistent asthma and this, together with a greater appreciation of their shared pathophysiology, has led the World Health Organization to promote the idea of 'one airway, one disease'—i.e., that allergic rhinitis and asthma are different manifestations of the same disease.

Considerable time and resources are expended on educational interventions for health-care professionals, both in the United

Kingdom and internationally, but despite these investments their impact on patient outcomes is still unknown. This is because such interventions are rarely evaluated beyond simple measures of satisfaction completed by the attendee, with little or no assessment of whether there is any impact on clinical practice or benefits to patients. Any intervention requiring time and/or financial commitment should be subject to the same rigorous evaluation as any other pharmacological or non-pharmacological intervention, and this is particularly true in financially constrained times. More specifically, the management of people with seasonal allergic rhinitis (and allergic rhinitis more generally) has been highlighted as being suboptimal by a number of studies^{11,12} and guidelines,⁸ with these inadequacies resulting in substantial—potentially avoidable—morbidity and cost. The overwhelming majority of people with seasonal allergic rhinitis are managed in the community;¹³ hence, this sector needs to be the focus of any attempt to improve the quality of care and outcomes.²

In an earlier multicentre randomised controlled trial,¹⁴ it was demonstrated that a part-time 6-month diploma-level allergy course was acceptable to attending primary health-care professionals, led to changes in relevant process measures (such as knowledge and confidence) and, importantly, translated into

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significant improvements in validated measures of disease-specific quality of life in adults. Although effective, many primary health-care professionals found this length of training difficult to incorporate into their practice, which raises important questions about the wider generalisability and sustainability of this approach. Following the approach advocated by the Medical Research Council's Framework for Complex Interventions,^{15,16} we used our experiences from this earlier trial and related work on the training needs of primary care professionals in the context of managing seasonal allergic rhinitis to inform the development of the current intervention.^{12,17,18} In seeking to mirror the ways in which the majority of UK health-care professionals receive their continuing professional education, we developed an intensive, evidence-based 1-day educational training intervention for primary care professionals. We then sought to evaluate the effectiveness of this training intervention for primary care-based health-care professionals on adolescent disease-specific quality of life.

MATERIALS AND METHODS

Overview of study design

We conducted a cluster randomised controlled trial of an educational intervention, which involved randomising general practice staff to receive either evidence-based allergy training or to the control arm in which practices received written guidance on the evidence-based management of seasonal allergic rhinitis.¹⁹ We chose a cluster randomised controlled trial, as a parallel group trial design would have resulted in a high risk of contamination. In keeping with recommended practice, our trial protocol and detailed analysis plan were reported before the closure of the trial;²⁰ any deviations from the methods described in the protocol are detailed below.

Setting and participants

This trial took place during the summers of 2009 and 2010 in 38 general practices within the recruitment areas of the Scottish Primary Care Research Network and England's Northern and Yorkshire Research Network. Scottish Primary Care Research Network and England's Northern and Yorkshire Research Network invited general practices to take part by email and letter. Each consenting practice was asked to nominate a member of their team to participate who had not received postgraduate allergy training in the previous 12 months. All patients aged 12–18 years with current seasonal allergic rhinitis were eligible to participate. We defined current seasonal allergic rhinitis by the presence of a documented clinician diagnosis in the patient's electronic health record and any evidence of treatment(s) used for seasonal allergic rhinitis in the last 2 years.²¹ Patients who fulfilled these criteria were invited to take part in the trial via a letter from the practice, which included a participant information sheet, consent form and reply envelope for return directly to the research team.

Randomisation and blinding

Practices were stratified on the basis of each of six regions: NHS Lothian; NHS South of Tyne and Wear; NHS North of Tyne; NHS County Durham; NHS North Yorkshire and York; and NHS Leeds; for regions where there were more than two clusters, a centrally administered minimisation scheme²² based on practice size and deprivation score was applied. Patients were masked to the allocation; however, it was not possible to mask the general practices as the intervention was attendance at a training workshop.

Intervention

Education for Health (<http://www.educationforhealth.org.uk/>) is one of UK's leading independent national training organisations offering accredited allergy training for professionals. We worked with Education for Health to develop an intensive 1-day evidence-based workshop, which was customised to meeting the needs of adolescents (see Box 1). The intervention consisted of an intensive study day focused on the diagnosis and management of young people with seasonal allergic rhinitis. The programme began with an assessment of the participant's current allergy

Box 1 Main topics covered in the seasonal allergic rhinitis training workshop

- History taking
- Diagnosis
- Treatment and management of allergic airways
- Identification and management of relevant co-morbidities
- Compliance and nasal spray device technique
- Organisational issues

knowledge, followed by the presentation of a case study, a discussion about the importance of getting the diagnosis of allergy correct and reasons for treatment failure. This was then followed by a brief overview of the pathophysiology of allergy in general, before moving into a more detailed discussion of this in the context of seasonal allergic rhinitis and asthma. Embedded within the programme were practical sessions on nasal spray and inhaler device technique. Delegates were given a copy of the British Society of Allergy & Clinical Immunology allergic rhinitis algorithm,¹⁹ and all treatment discussions were based on the World Health Organization's Allergic Rhinitis and Asthma²³ and British Thoracic Society/Scottish Intercollegiate Guidelines Network (<http://www.sign.ac.uk/guidelines/full-text/101/index.html>) guidelines on the management of allergic rhinitis and asthma, respectively (current at the time of the study). There was ample time for individual and group discussions to ensure that individual learning styles were catered for and any queries were addressed.

Health-care professionals (1 general practitioner and 19 practice nurses) nominated by the general practices who were randomised to the intervention arm attended these 1-day intensive workshops delivered by experienced Education for Health trainers. The course was repeated on five occasions.

Control group

Health-care professionals (again nominated by the practices and in this case all nurses) in the control practices received an allergic rhinitis algorithm developed by the British Society of Allergy & Clinical Immunology,¹⁹ which was adapted for use in primary care by Education for Health. No training was offered to the 18 health-care professionals randomised to the control arm.

Objectives and outcomes

Our primary outcome of interest was the difference in the change in adolescents Standardised Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)) score between baseline and 6 weeks post intervention in the intervention arm compared with the control arm. Consenting patients completed the RQLQ(S) and a symptoms score, which was measured on a 10-point visual analogue scale. Data were collected from two cohorts of patients in two separate years: 2009 and 2010. Baseline RQLQ(S) and symptom scores were recorded in May and early June 2009/2010; patients were then seen by their health-care professional, and follow-up RQLQ(S) and symptom scores were recorded in late June and July 2009/2010 (i.e., during the peak of the grass pollen season).

Our secondary outcomes of interest were:

- Assessment of change in clinical practice among the health-care professionals allocated to the intervention arm: the effects of the 1-day training on self-reported professional confidence, and understanding and clinical management of seasonal allergic rhinitis, which were measured immediately before and after the training days, and after all the patients taking part in the study had been seen by a health-care professional (~7–28 days), using a questionnaire that incorporated a 5-point Likert scale (1 = less confident and 5 = more confident).
- Total number of consultations for seasonal allergic rhinitis.
- Total number of prescribed medications for seasonal allergic rhinitis.
- Patient-reported symptom scores.

Pollen data

Grass pollen data from York and Edinburgh (which covered the areas from which practices were drawn) were centrally provided by the National Pollen and Aerobiology Research Unit for 2009 and 2010 in order to assess whether the pollen counts reached a level that was likely to trigger

seasonal allergic rhinitis symptoms during the study period. The pollen count is a measure of the number of pollen grains per cubic metre (pg/m^3) of air sampled, averaged over 24 h.

Sample size calculations

We calculated that a target sample size of 220 would give 80% power to detect a mean difference of 0.5 in RQLQ(S) score—the minimal clinically important difference at the 5% significance level. This was calculated using Sampsize^{24} assuming an s.d. of 1.2²⁵ and intraclass correlation (ICC) of 0.02. There is little evidence in the literature of the likely size of the design effect from clustering in trials of this kind, and the choice of the relatively low ICC value of 0.02 was based mainly on the finding of no evidence of clustering in our earlier adult study using RQLQ.¹⁴

Statistical analysis

We undertook a complete case analysis for our main analysis. In the primary analysis, multilevel modelling using a random effects model was used to take account of between- and within-cluster variation, adjusting for strata, individual covariates and year of study. Estimates and confidence intervals of the intervention effects are reported for the RQLQ(S) and symptom score.

Consultation and prescribing data were collected from the participating general practices for all patients from the date of consultation for the study to 31 August 2009/2010. Differences between the two groups were analysed using multilevel analysis in MLWin (version 2.20, 2010, <http://www.bristol.ac.uk/cnm/software/mlwin/>).

Differences in the mean scores of self-reported confidence and understanding of seasonal allergic rhinitis management in the intervention group were compared using t-statistics.

We first used mixed-model analysis of variance (ANOVA) using SPSS (version 14, 2005, SPSS, Chicago, IL, USA) to estimate the ICC for RQLQ(S), followed by a Bayesian approach using WinBUGS (version 1.4, 2009, <http://www2.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml>), taking a uniform prior over 0–1.²⁶

Deviations from the trial protocol

Educational data. We were unable to collect educational data because of time constraints resulting from the delays in recruiting practices.

Follow-up RQLQ(S). Follow-up primary outcome data were collected by post and the majority were collected 6 weeks post intervention as planned and described in the trial protocol;²⁰ however, there were a small number of questionnaires collected between 6 and 8 weeks post intervention as a result of non-responders to the initial mailing and the need to issue reminders.

Missing data. Our complete case analysis provided unbiased estimates under the assumption that the missing data are 'Missing Completely At Random';²⁷ however, analysis of the means estimated separately for each pattern of missingness suggested that this assumption may not hold. We therefore carried out further sensitivity analyses testing a variety of assumptions:

- The direct likelihood method;²⁸ the primary analysis of the effect of the intervention on RQLQ(S) was repeated, but with the baseline score modelled jointly with the outcome at 6 weeks instead of entering the model through the linear predictor. This model allowed for the inclusion of all 309 patients with data on at least one occasion and provided likelihood-based estimates that are valid under 'Missing At Random'²⁷ (under the assumption that the responses are multivariate normal).
- Multiple imputation: Proc MI in SAS (SAS Institute, Cary, NC, USA) was used to generate multiple imputations separately for each treatment arm (pooling across centres) ($m = 100$ imputations).
- Alternative scenarios under 'Missing Not At Random'²⁷ for poor and good outcomes: first, under a poor outcome assumption, we imputed missing values in any particular cluster (at baseline or follow-up) using the largest observed score from that cluster (and time point). Second, under a good outcome assumption, we used the lowest observed scores from each cluster (and time point) to impute missing values.

RESULTS

Baseline characteristics

Thirty-eight general practices (clusters) agreed to participate in the study, of which 20 were randomised to the intervention arm and 18 to the control arm. Of the patients assessed for eligibility from the general practice medical records, 1,565 satisfied our inclusion criteria and, of them, 341 agreed to participate (see Figure 1).

Participating ($n = 38$) and non-participating practices ($n = 204$) had comparable demographic characteristics. In Scottish sites, the mean and s.d. of list size for participating practices was 6,562 (3,363) and that for non-participating practices was 6,971 (3,302) ($P = 0.75$); the mean deprivation quintiles were 2.69 (s.d. 0.67) and 2.60 (s.d. 0.70) ($P = 0.76$), respectively. In English sites, the mean list size for participating practices was 8,707 (s.d. 4,048) and for non-participating practices 7,464 (s.d. 4,847) ($P = 0.19$); the Index of Multiple Deprivation scores were 26.8 (s.d. 18.2) and 31.0 (s.d. 19.6) ($P = 0.27$), respectively.

Clusters were comparable for baseline characteristics in terms of deprivation; however, the intervention practices had a larger mean list size (see Table 1). Participants were comparable at baseline in terms of age and sex profiles.

Primary outcome: impact on seasonal allergic rhinitis quality of life

A total of 246/341 patients (50.2% male, mean age 15 years) were included in the primary outcome analysis. The intervention failed to result in a clinically important improvement in RQLQ(S) (−0.15, 95% confidence interval (CI), −0.52 to +0.21) (adjusted for baseline RQLQ(S)), practice list size and region, year of study and deprivation.²⁹

Secondary outcomes

Assessment of change in clinical practice. Health-care professionals' self-assessment of their confidence and understanding of seasonal allergic rhinitis management markedly increased post intervention when compared with the baseline assessment (see Table 2). All scores improved from Time 1 (immediately before the training day) to both Time 2 (immediately after the training day) and Time 3 (after all patients had been seen as part of the study).

Consultation and prescribing data. Five of the 38 practices did not provide data on consultation and prescribing patterns (three control and two intervention arm practices). Table 3 summarises data revealing that the intervention arm practices tended to have more consultations and prescriptions in total, and also more consultations for other respiratory conditions, but that the figures for seasonal allergic rhinitis did not differ greatly between the two arms.

Grass pollen and symptom score data. Figure 2 indicates that the grass pollen reached sufficiently high counts (50–149 pg/m^3) at both sites in both years to induce seasonal allergic rhinitis symptoms and that there was no significant regional variation between the two collection sites. Adjusted symptom scores in the intervention group were slightly lower than in the control group (−0.24, 95% CI, −1.03 to +0.54).

Estimates of ICC

The ICC was estimated as 0.034 after adjusting for baseline RQLQ and the intervention group, with a 95% credible interval of 0.0016–0.145.

Sensitivity analysis for impact on quality of life

By using the direct likelihood method²⁸ to account for the missing data under a Missing At Random mechanism, the (adjusted) effect of the novel intervention on RQLQ(S) at 6 weeks was found to be

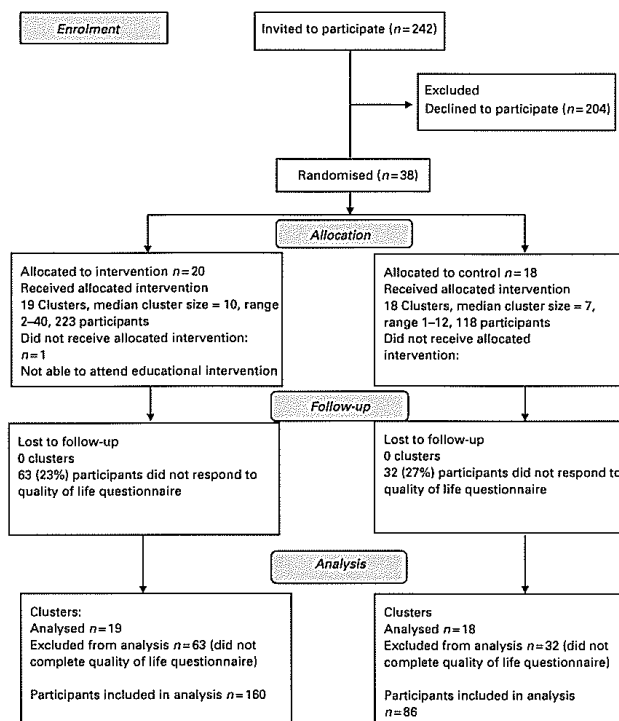


Figure 1. Flow of clusters and patients through the trial.

	Intervention arm	Control arm
Practice factors		
Number of clusters	20	18
Mean list size	11,144	8,330
Mean deprivation score		
IMD ^a	21.5	21.7
SIMD ^b	2.48	2.47
Patient factors		
Number	223	118
Mean age (years) (s.d.)	15 (1.85)	15 (1.91)
Number (%) male	112 (50.2)	57 (48.3)

^aIMD—The 2004 Index of Multiple Deprivation for English practices.
^bSIMD—Scottish Index of Multiple Deprivation.

0.03 (95% CI, −0.33 to 0.39), supporting the finding that there is no beneficial effect of the intervention on RQLQ(S) score.

We obtained similar results with multiple imputation methods based on 100 imputed data sets. Using multiple imputations to account for the missing data, the intervention effect was 0.06 (95% CI, −0.30 to 0.42).

Finally, under the poor outcomes scenario, imputing missing data using large RQLQ(S) values, the estimated effect of the intervention was 0.21 (95% CI, −0.21 to 0.63). Under the good outcomes scenario, using low RQLQ(S) values to impute the missing data, the estimated intervention effect was 0.03 (95% CI, −0.39 to 0.44). The conclusions were thus unchanged: the intervention failed to have the desired effect.

DISCUSSION

Main findings

This large general practice-based cluster randomised controlled trial has shown that a short intensive evidence-based allergy workshop for health-care professionals led to substantial and persistent improvements in their self-reported confidence and understanding of the management of seasonal allergic rhinitis, but this did not translate into changes in clinical practice in terms of frequency of consultations or prescribing habits; most importantly, this did not lead to clinically significant improvements in disease-specific quality of life or symptom score in adolescents with seasonal allergic rhinitis.

Strengths and limitations of this study

The main strength of this trial was the decision formally to evaluate this evidence-based educational intervention using an adequately powered cluster randomised controlled trial, which is most

Table 2. Audit of confidence in delivering allergy care (n = 21)

Question	Time 1 ^a	Time 2 ^a	Time 3 ^a	95% CI ^b
<i>How confident are you at</i>				
Taking a comprehensive allergy history from a patient with suspected allergy?	2.6	4.2	4.4	1.0, 2.2
Doing skin prick testing?	1.1	2.7	2.4	0.4, 2.6
Ordering specific IgE test?	1.5	3.8	3.5	1.2, 2.8
Making a diagnosis of allergy?	2.1	4.4	4.3	1.6, 2.7
Explaining the various effective treatment strategies for allergic problems?	2.2	4.3	4.7	1.9, 2.9
Prescribing/recommending treatment for allergic conditions?	2.3	4.1	4.6	1.4, 2.8
Teaching patients how to use nasal spray devices?	2.3	4.7	5.0	1.9, 3.2
Explaining the causes and mechanisms of allergy?	2.4	4.2	4.5	1.4, 2.7
Understanding the impact of allergy on morbidity and mortality?	2.6	4.2	4.5	1.4, 2.7
<i>How likely are you to do the following</i>				
Ask about other allergic symptoms (e.g., nose/skin) when assessing a patient with asthma?	3.3	4.8	4.8	0.6, 2.0
Consider total steroid use in patients on multiple therapies?	2.6	4.2	4.1	1.0, 2.2
Offer practical advice on avoiding allergens?	3.1	4.8	4.9	1.0, 2.4
Suggest patients use their nasal steroids regularly?	3.1	4.9	5.0	1.3, 2.5

Abbreviation: CI, confidence interval.

^aTime 1—immediately before the training day, Time 2—immediately after the training day, Time 3—after all patients had been seen as part of the study (range 7–28 days).^b95% CI for change in mean score from Time 1 to Time 3.

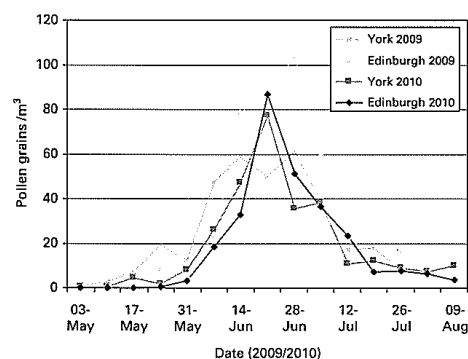
uncommon. We developed a complex intervention based on a previous effective educational intervention for health-care professionals and measured the effectiveness of this on a validated disease-specific quality of life measure; in keeping with the Medical Research Council's complex intervention framework,¹⁶ we also measured a range of relevant process measures, which aimed to shed light on the mechanisms through which any changes were mediated and/or blocked. We have demonstrated the acceptability of the intervention and that it has an impact on professionals' self-assessed confidence and knowledge of seasonal allergic rhinitis management, but that the intervention did not equip individuals with the ability to enact relevant structural changes in their practices to translate this into improvements in care processes.

We conducted a complete case analysis supplemented by sensitivity analyses to assess the likely impact of the missing data. Our sensitivity analyses strengthened our finding of no beneficial effect of the intervention on RQLQ(S). A limitation of this study may be that patients in the control arm of the cluster trial also consulted with a health-care professional, which it could be argued may not reflect routine primary care. It was necessary to

Table 3. Consultation and prescribing data

	Intervention arm, n = 193	Control arm, n = 88	95% CI ^a
Total (and mean per patient) number of consultations ^b	200 (1.04)	85 (0.97)	−0.02, +0.63
Total (and mean per patient) number of rhinitis consultations ^b	55 (0.28)	29 (0.33)	−0.24, +0.08
Total (and mean per patient) number of consultations for other respiratory conditions ^b	27 (0.14)	8 (0.09)	−0.01, +0.22
Total (and mean per patient) number of prescriptions ^b	557 (2.89)	197 (2.24)	+0.08, +2.15
Total (and mean per patient) number of prescriptions for rhinitis ^b	406 (2.10)	140 (1.59)	−0.10, +0.12

Abbreviation: CI, confidence interval.

^a95% CI for difference in mean between intervention and control groups.^bCumulative total for all patients from the date they were seen for the trial consultation to 31 August 2009 or 2010.**Figure 2.** Pollen count in 2009/2010. Notes: The pollen forecast is usually given as low (< 30 pg/m³), moderate (30–49 pg/m³), high (50–149 pg/m³) or very high (150 pg/m³). pg, pollen grains

design the study this way in order to understand the cause of any potential effectiveness of the educational intervention and to be able to distinguish this from any impact of simply being seen for seasonal allergic rhinitis. Control arm practices received an algorithm and information leaflet for the management of seasonal allergic rhinitis, both of which were adapted by Education for Health. One way of disentangling this issue would have been to include a third arm in which practices received no intervention; however, this was not possible within the constraints of this trial. An additional possible limitation of this study is that cluster sizes were not balanced. We used general practice list size in the minimisation scheme; we may, however, have reached a better balance in clusters if we had used number of adolescents, as this varied between clusters more than we had anticipated. The effect of this imbalance on the power of the study was small, and we still achieved the power required.

Interpretation of findings in relation to previously published work. Patients in this study had on average relatively mild impairment of quality of life measured by the RQLQ(S), which is in line with a similar study exploring the quality of life of perennial rhinitis sufferers.¹⁴ Patients were recruited from a primary care setting, using a clinician diagnosis of seasonal allergic rhinitis or a prescription for drugs used in nasal allergy in the last 2 years, rather than objective evidence of moderate or severe disease. As also observed in our earlier perennial rhinitis trial,¹⁴ the impact of this training intervention may have been more evident if we had restricted trial entry to those with more severe disease. This would, however, have reduced the generalisability of the intervention to everyday general practice.

We would have expected more consultations in the intervention group if the training had achieved a sustained change in clinical practice, but this was not the case. The training days were delivered by practising health-care professionals and based on current evidence-based guidelines for the management of seasonal allergic rhinitis developed by the British Society of Allergy & Clinical Immunology.¹⁹ The prescribing data included all repeat prescriptions; therefore, if the intervention practices followed the guidance given in the workshop, patients with persistent symptoms would be receiving an antihistamine, nasal steroid and/or topical ocular treatments, as appropriate.

Implications for future research, policy and practice

Future trials need to build on the findings of both this and our earlier trial,¹⁴ and find ways of equipping participants of such short courses with the skills necessary to bridge the gap between knowledge and day-to-day practice. A key consideration is not only to upskill primary care-based health-care professionals but also to develop their ability to effect organisational change. The increasing opportunities for blended learning—i.e., a combination of both face-to-face and virtual training—should also provide opportunities for periodic, convenient and accessible reinforcement of key messages. Developing such initiatives and then formally trialling their effectiveness is important to help ensure that the National Health Service and other health-care systems internationally invest their limited resources in evidence-based educational interventions of proven effectiveness.

Conclusions

In conclusion, this intensive seasonal allergic rhinitis training workshop for primary care health-care professionals was found acceptable and increased self-assessed confidence in attendees, but this did not translate into improvements in symptom control or quality of life of adolescents with seasonal allergic rhinitis.

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The views presented here are those of the author and not necessarily those of The Commonwealth Fund, its directors, officers, or staff.

CONTRIBUTIONS

AS, SW and VSH conceived and managed the trial, AS is the guarantor. RAE provided statistical and methodological advice in designing the trial, CHH carried out *post hoc* sensitivity analysis. VSH was the researcher employed on

this project and led the drafting of this manuscript. All authors commented on draft versions and read and approved the final manuscript.

COMPETING INTERESTS

SW is an Associate editor of, and AS is Joint Editor-in-Chief of, the PCRIJ. Neither were involved in the editorial review of, nor the decision to publish, this article. All other authors declare no conflict of interest.

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Seasonal Allergic Rhinitis search strategy paper

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ORIGINAL RESEARCH

Developing and testing search strategies to identify patients with active seasonal allergic rhinitis in general practice

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Abstract

Aim: We sought to assess the accuracy of different search terms to identify individuals with active seasonal allergic rhinitis (SAR) in general practice.

Methods: A reference search strategy was developed to identify patients with active SAR. This was applied through inspection of electronic health records of patients aged 15-45 years in a 10% random sample of a general practice database. Searches used Read codes and medication relating to SAR. Sensitivity, specificity, and positive and negative predictive values were calculated.

Results: Using the reference search strategy, 54/1092 (4.9%) of 15-45 year-old patients had current SAR. Searching for drugs used in nasal allergy had the highest sensitivity (85%) and good specificity (86%). Searching for a recorded history of SAR (H170) in the last two years was more specific (100%) but this approach only had limited sensitivity (17%).

Conclusions: Electronic searches can be used to identify patients with current SAR, but the accuracy varies widely. Larger numbers of sufferers can be identified using broader search parameters, but with increasing numbers of false positives. In contrast, more focused search strategies give a smaller yield needing less cleaning of data to identify true positives, but there is an associated increase in the number of false negatives.

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Keywords seasonal allergic rhinitis, general practice, electronic search, Read codes, medication

See linked editorial by Levy on page 11

The full version of this paper, with online Appendix, is available at www.thepcrj.org

Introduction

Seasonal allergic rhinitis (SAR) is common in the UK and is responsible for considerable morbidity, impairment in quality of life and healthcare utilisation.¹ It has recently been shown to be associated with impaired educational attainment in adolescents.²

The Allergic Rhinitis in Asthma (ARIA) classification scheme was introduced in 2001 and reinforced in 2008; this subdivides allergic rhinitis into "intermittent" or "persistent" disease.^{3,4} Previously, based on time of exposure, allergic rhinitis was subdivided into "seasonal" (more commonly known as hayfever), "perennial" and "occupational" forms. Intermittent

allergic rhinitis (IAR) is defined as symptoms being present for less than four days per week for less than four weeks, and persistent allergic rhinitis refers to symptoms that are present for more than four days a week and for more than four weeks. Although this clinical definition is officially accepted in the UK as in other countries, the classification has not yet been widely adopted in UK primary care, and patients with IAR are thus still given a Read code⁵ for seasonal allergic rhinitis in their computerised medical records. Hence, these terms and codes need to be searched when identifying local populations.

There is a need for increased research into SAR in order to improve understanding of its aetiology, changing epidemiology, disease trends and possible interventions to improve outcomes in people with SAR.^{6,7} For example, one study currently being undertaken is a large cluster randomised trial of an educational intervention for adolescent hayfever sufferers, where it was

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crucial to identify accurately participants for recruitment using electronic health records. Undertaking such work in primary care populations is important because of the opportunity to generate research findings that will be directly applicable to the general practice setting in which the majority of UK patients with SAR are currently managed.

In countries where the vast majority of primary care practices use electronic health records, novel primary care database searching methods using appropriate history and medication codes potentially provide an efficient means to identify such patients.⁵ However, problems remain, such as the diversity of clinical computing systems and the inconsistent use of coding schemes by clinicians.⁸

Internationally, several medical coding systems exist.⁸ However, for allergic rhinitis the codes are reasonably interchangeable between various systems. For example, the International Classification of Disease-10 code J30.1 (due to pollen) and the International Classification of Primary Care-2 R97 (hayfever/allergic rhinitis) will potentially identify the same patients as H170 (seasonal allergic rhinitis), the Read (5-byte version 2) coding scheme used in this pilot. Date ranges included in a search strategy can be adjusted for the relevant aeroallergens of a particular country. Previous work in other diseases^{9,10} suggests that search strategies should be bespoke, reflecting differences in clinical and coding definitions nationally and internationally.

The utility of the various search strategies available is currently unknown. In order to investigate the relative accuracy of different search approaches, we sought to assess the sensitivity, specificity, and positive and negative predictive values associated with a range of search strategies in the context of identifying patients with current SAR.

Methods

Ethics and research management approval

Formal ethics and research management approval were not required as the research was undertaken using an anonymised dataset. [Dodds P. Personal communication, 4.6.09] Approval was obtained from the practice prior to commencing the fieldwork.

Setting and sampling

Our pilot study was carried out at a large three-site UK general practice with a list size of 32,436 patients served by 17 general practitioners (GPs). For the last four years, medical records – including all consultations and prescribing – have been recorded in an electronic health record ("Vision"™, In Practice Systems Ltd.) which is based on 5-byte Read codes (version 2). Read codes are organised in a hierarchical manner. For example, allergic rhinitis is coded as H17, and SAR is coded as H170; searches using H17 will thus include all people with SAR and other types of rhinitis, including

perennial rhinitis, whereas searching H170 will only include those people with a specific diagnosis of SAR.

We selected all patients aged 15-45 years ($n=10,920$) and from this sample selected a random 10% sample of records for detailed manual interrogation ($n=1,092$) against the reference search strategy employed. This 10% sample was also used for all the test search strategies thereby allowing a direct comparison with the reference search strategy.

Reference search strategy

The reference definition used was:

- The presence of the SAR Read code (H170) as a history item or active problem recorded in the individual patient's electronic record or in the active problem field applied within the last two years, AND/OR
- A consultation with a clinician within the last two years diagnosing SAR (in free text or otherwise), AND/OR
- A diagnosis of SAR in the free text ("hay fever", "rhinoconjunctivitis", "SAR", "pollen allergy") OR H170 Read code applied previously (i.e. over two years ago) and a current prescription during the "hay fever" season for drugs used in treating SAR (nasal corticosteroids, sodium cromoglicate eye drops or antihistamines – checking that antihistamines and other drugs had not been given for any other condition).^{11,12}
- The "hay fever season" was defined as "01.05.08 – 31.07.08 or 01.05.09 – 31.07.09" inclusive.¹³ The SAR season date ranges in searches were linked using the "OR" command.

Test search strategies approval

Three search strategies were tested:

- 1) based on Read codes suggestive of SAR
- 2) medication prescribed for treatments that can be used in SAR
- 3) a combination of the Read codes and medication prescribed.

Details of these test search strategies are reproduced in Appendix 1, available online at www.thepcrj.org.

Statistical techniques

We used the principles of the approach advocated in the

Box 1: Definitions of tests used

Sensitivity: The proportion of true positives that are correctly identified by the test

Specificity: The proportion of true negatives that are correctly identified by the test

Positive predictive value: The proportion of patients with positive test results who are correctly diagnosed with a search strategy

Negative predictive value: The proportion of patients with negative test results who are correctly diagnosed with a search strategy

STARD guidelines.¹⁴ This involved calculating the following test parameters: test accuracy; sensitivity and specificity; and positive and negative predictive values (see Box 1 for details). Analysis was undertaken using Microsoft Excel software.

Results

Applying the reference search strategy

Applying the reference approach was a very labour-intensive process. Manually searching the electronic health records of the 1,092 records in the sampling frame took approximately 30 hours. These searches yielded 54 (4.9%) true positives, equating to approximately 33 minutes per case identified.

Accuracy of test search strategies

It was possible to execute successfully all the planned search strategies. The accuracy of the various test strategies employed is summarised in Table 1. The key findings were:

- 1) Searching on a specific SAR code recorded in the previous two years was 100% specific but the sensitivity was only

Table 1. Code and drug search results on 10% random sample of the 15-45 year old population.

Codes	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Code only (last 2 years)				
H17 (Allergic rhinitis)	0.22	1.00	1.00	0.96
H170 (SAR)	0.17	1.00	1.00	0.96
Drug group only				
Antihistamines (3.4.1)	0.78	0.86	0.22	0.99
Corticosteroids (6.3)	0.26	0.92	0.15	0.96
Other anti-inflammatory preparations (cromoglicate)	0.43	0.96	0.38	0.97
Drugs used in nasal allergy	0.85	0.86	0.24	0.99
Drug combinations (2 SAR seasons)				
Sodium cromoglicate OR nasal allergy drugs	0.41	0.98	0.55	0.97
Sodium cromoglicate OR antihistamines	0.61	0.98	0.62	0.98
Sodium cromoglicate corticosteroids	0.35	0.96	0.31	0.97
Antihistamines or corticosteroids	0.59	0.94	0.35	0.98
Antihistamines or drugs used in nasal allergy	0.67	0.97	0.50	0.98
Corticosteroids or drugs used in nasal allergy	0.54	0.95	0.34	0.98
Any drug	0.67	0.94	0.36	0.98
All drugs and Read code H170 (last 2 years)	0.72	0.93	0.35	0.98

17%. The high positive and negative predictive values points to the efficiency of this approach. Such a search strategy would therefore be ideal for highlighting a small number of patients who are very likely to have SAR. However, it would not be useful for identifying the whole SAR population since 83% of patients were missed.

- 2) In contrast, searching for drugs used in nasal allergy had high specificity, sensitivity and negative predictive values, but low positive predictive values, indicating that this approach is particularly useful for identifying the largest number of potential SAR cases – although this would entail some cleaning of data to exclude false positives.
- 3) The combination of drugs used in nasal allergy and/or a SAR Read code (H170) during the previous two seasons had a 72% sensitivity and a 93% specificity, indicating that it may be useful for identifying large numbers of those with SAR whilst reducing the time requirement for data cleaning. There would be a trade-off between time required to identify the 7% of false positives versus the number of SAR positive individuals required for the study.

Discussion

This study has, for the first time, demonstrated the different yields of patients with current SAR identified by conducting different search strategies to interrogate GP records. We hope that our work will inform clinicians and researchers and enable them to reflect critically on the search strategies employed to identify patients with SAR and also to begin to understand the resource implications for cleaning data associated with employing different search strategies.

Strengths and limitations of this work

One of the main strengths is that all potentially eligible patients were equally likely to be studied; there was therefore no risk of selection biases.¹⁵ Another strength of the design is that it was based on clinician-diagnosed SAR, not on self-reporting by patients with current or historical symptoms, although this may have had a significant impact on the estimated population prevalence in the practice database as a result.

The major limitations include the fact that the reference and test assessments were conducted by one researcher, although in order to mitigate against the possible risks of misclassification error, clear protocols and explicit criteria were consistently used. Also, this work was only undertaken in one general practice, albeit a very large practice, raising the possibility that practice idiosyncrasies in coding could limit the generalisability of this work. For example, sodium cromoglicate was included in the search strategy as in this particular practice this is the only drug from this drug group in the practice formulary prescribed for hayfever. However, other drugs within BNF group 11.4.2 (other anti-inflammatory preparations) may need to be included in other general practice searches. There is

therefore a need to replicate this work in other practices to assess the robustness of our test statistics. A few treatments (specifically montelukast) licensed for the treatment of SAR were excluded from our search strategy as they are not included in the relevant BNF groups. These drugs are not in this practice's formulary for the treatment of SAR, and are therefore rarely used for this indication – so exclusion from our searches will have had little effect on our findings. There is also the limitation that up to half of the patients with SAR may be self-diagnosed and hence neither known to, nor coded by, their GP.¹⁶ This constraint, whilst important, cannot currently be overcome through interrogation of practice electronic health records.

Conclusions and recommendations for research

There is clearly no "ideal" search strategy, due to the trade-off between specificity and sensitivity. If the clinician or researcher needs to identify a small number of people definitely suffering from SAR, then a search for the H170 code will identify such people most efficiently. Time-limiting these searches to the last two years, for example, will allow the identification of those with current SAR.

To identify the largest possible population of SAR sufferers, the names of all drugs used to treat nasal allergy should be incorporated into the search strategy. Potentially, this strategy could be improved further by integrating general practice and pharmacy computer systems to take account of over-the-counter prescriptions. However, cleaning the results of such a search to remove false positives is a labour- and time-intensive process, and so this is only likely to be appropriate for large scale, well resourced projects.

More broadly, in the UK, management of some long-term conditions (e.g. asthma) now attracts incentive payments under the Quality and Outcomes Framework (QOF), which is dependent on consistent coding. If, in the future, SAR were to be adopted as an indicator within QOF, coding would very likely improve.

Finally, the Read code system has inherent limitations. Often, useful information is written in the free text within the medical record. A final recommendation, therefore, would be the ability to carry out free-text searches on individual patient medical records. A method by which one could search for that free text, such as "natural language searching", would facilitate investigation of a large number of records, more so with patients who have long and complex medical histories.¹⁷

Conflict of interest declarations

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Appendix 1. Read codes and drugs used in searches.

Read Code:	Definition:
H17..	Allergic Rhinitis
H170.	Seasonal Allergic Rhinitis

Drug groups used in nasal allergy (BNF 57, 2009)

B.N.F. Drug Group:	Drug:
Nasal corticosteroids	Beclometasone Dipropionate
	Betamethasone Sodium Phosphate
	Budesonide
	Flunisolide
	Fluticasone Propionate
	Mometasone Furoate
	Triamcinolone Acetonide
Antihistamines	Alimemazine Tartrate
	Chlorphenamine Maleate
	Clemastine
	Cyproheptadine
	Hydrochloride
	Hydroxyzine Hydrochloride
	Ketotifen
	Promethazine Hydrochloride
	Cetirizine Hydrochloride
	Desloratadine
	Fexofenadine Hydrochloride
	Levocetirizine Hydrochloride
	Loratadine
Cromoglicate	Sodium Cromoglicate 2% W/V Eye drops

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Is it unfair to hayfever sufferers to have to sit examinations during periods of high pollen counts?

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“Hayfever ... has the potential to disrupt students both when revising for and sitting examinations, which has led some quarters to call for the timing of examinations to be changed.”

Crucial examinations take place during adolescence in most societies, which can have a major impact on an individual's career trajectory. Examination boards have recognized that some health problems can impact on a student's ability to perform in examinations and in response have introduced measures to take account of this – for example, offering extra examination time for students with dyslexia. However, this is not yet generally the case in relation to students with hayfever (also known as seasonal or intermittent allergic rhinitis). This is concerning since, in the UK, critical examinations for children 15–18 years of age take place over a 6-week period during May and June when grass pollen counts are typically at their highest (see FIGURE 1) [1]. Also of relevance is that tree pollens tend to peak from late February to the middle of May when students are likely to be revising for their examinations. Hayfever thus has the potential to disrupt students both when revising for and sitting examinations, which has led some quarters to call for the timing of examinations to be changed. In this article, we review the evidence of the disease burden associated with hayfever and summarize recent evidence that suggests that poorly controlled hayfever can adversely impact on examination performance, drawing on these data to reflect on the question of whether students with hayfever are indeed unfairly

disadvantaged by being forced to prepare for and sit examinations during the peak of the pollen season.

Defining & categorizing allergic rhinitis

Rhinitis refers to inflammation of the nasal lining and tends to manifest with symptoms of sneezing, rhinorrhoea, nasal itch and nasal blockage/congestion; conjunctival symptoms are often present, particularly if the underlying etiology is allergic in origin [2]. Allergic rhinitis refers to IgE-mediated disease in which exposure to aeroallergens in previously sensitized people results in mast cell degranulation and the release of inflammatory mediators. These allergic triggers can be seasonal, including tree, grass and weed pollens and mold spores, or perennial, this latter category including house dust mite and animal dander. The seasonal variety is more commonly known as hayfever.

The Allergic Rhinitis in Asthma classification scheme, which is based on a combination of the frequency and severity of symptoms, was introduced in 2001 and reinforced in 2008; this subdivides allergic rhinitis into intermittent or persistent disease forms [3,4]. In the UK, intermittent rhinitis is virtually synonymous with the seasonal category or hayfever, although this overlap is far less clear in equatorial regions [5].

KEYWORDS: examinations • hayfever • performance • pollen • seasonal allergic rhinitis

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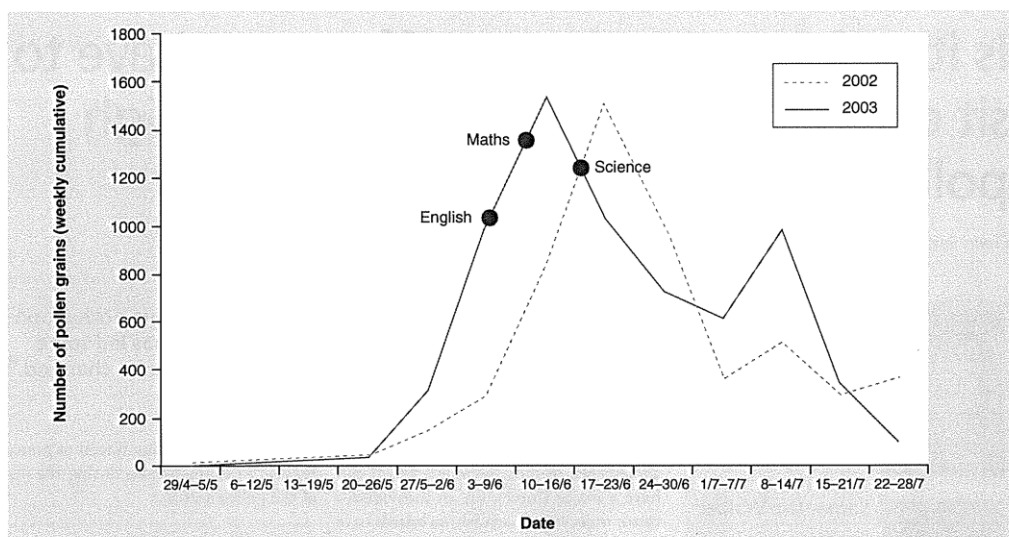


Figure 1. Grass pollen counts in central England in 2002 and 2003, with core General Certificate of Secondary Education examination dates from 2003 represented by circles.

Pollen counts courtesy of the National Pollen and Aerobiology Research Unit.

High prevalence & disease burden of allergic rhinitis

Allergic rhinitis is a global health problem affecting males and females of all ages from all ethnic groups and socioeconomic backgrounds. In the UK, allergic diseases currently have a lifetime prevalence of approximately 30% in the general population [6,7], although this proportion is projected to increase. Rhinitis is one of the most common allergic problems in young people [8], affecting 40% of 13–14-year olds [9]; it is closely followed by asthma, which affects approximately 30% of young people [9].

There are many national and international studies describing the prevalence of allergic rhinitis and its risk factors [3], many of these based on the International Study on Asthma and Allergy in Childhood [9], which aimed to describe the prevalence and severity of asthma, rhinitis and eczema in children examined at different centers and to make comparisons within and between countries over time. Phase III of the study was planned to assess time trends over a period of at least 5 years in the prevalence of symptoms by repeating the initial Phase I cross-sectional survey. Most centers showed a change in the prevalence of symptoms of allergic rhinoconjunctivitis for the age groups 6–7 and 13–14 years of age (80 and 70%, respectively). In both age groups the prevalence was found to have increased more often than it decreased [10]. Combined data from all centers showed that the proportion of children with symptoms of more than one of asthma, allergic rhinoconjunctivitis and eczema rose slightly from Phase I to Phase III.

Rhinitis and asthma frequently coexist, with population surveys estimating that up to 40% of all allergic rhinitis patients

have asthma and that up to 80% of people with asthma have rhinitis [11–13]. Other common comorbidities include allergic conjunctivitis, allergic sinusitis and eczema.

Allergic rhinitis causes a significant health burden to the individual, and the impairment of quality of life experienced by patients with rhinitis is at least as severe as that of patients with asthma [4]. It is known to reduce quality of life, can impair sleep and leisure activities and can reduce academic performance [14]. It can also cause bronchial hyperreactivity.

“...recent evidence ... suggests that poorly controlled hayfever can adversely impact on examination performance...”

Most of the economic analyses performed to date are based on US data; in 2003, the estimated annual costs of allergic rhinitis ranged from US\$2 to \$5 billion [15]. These estimates include indirect costs such as reduction in productivity, which are difficult to accurately estimate. In the UK, direct National Health Service costs for managing allergic problems were estimated at over £1 billion per annum [7]. The costs to society resulting from allergic rhinitis are believed to be increasing [16].

Evidence of a detrimental impact on education performance

Studies have shown that adults with allergic rhinitis experience a reduction in cognitive function and psychological well-being [17], and that children with symptomatic allergic rhinitis had

significant learning impairment (in a simulated educational setting) compared with asymptomatic controls [18]. This detrimental impact has been shown to be compounded by the use of sedating antihistamines [19]. A more recent study has shown that when compared with healthy controls, allergic rhinitis sufferers experience increased difficulty with tasks requiring sustained attention [20].

A study carried out in 2007 attracted much media attention, resulting in headlines such as: "Hayfever drugs cost students an exam grade" [21]. This large case-control study involving 1834 students investigated whether hayfever adversely impacts examination performance in UK teenagers. Walker *et al.* looked at the association between current symptomatic hayfever and rhinitis medication and the risk of unexpectedly dropping a grade in summer examinations when compared with the mock examinations [21]. For clarity, the normal expectation is that most students will achieve at least the same grade as achieved in their mock examinations – which mainly take place in the winter months – and so a drop in grade would thus be unexpected. The study showed that those who had hayfever symptoms on any examination day were more likely to drop a grade between their mock and final examination for maths, english and science (odds ratio [OR]: 1.43; 95% CI: 1.13–1.81; $p = 0.002$). This risk increased if students were taking a sedative antihistamine at the time of their examinations (OR: 1.71; 95% CI: 1.06–2.75; $p = 0.03$). Students with more severe hayfever, as measured by symptom scores on the day of the examination and a previous history of summer hayfever symptoms, were at an even greater risk of dropping a grade.

"...compared with healthy controls, allergic rhinitis sufferers experience increased difficulty with tasks requiring sustained attention."

Although this case-control study in naturally occurring populations adds important evidence of the potential bias against students with hayfever, more studies are needed to confirm this finding. This is because case-control studies are a relatively weak design for establishing the causality of the relationships. Importantly, there is currently no evidence of reversibility, which is one of the criteria used to infer a causal relationship between hayfever and a detrimental impact on examination performance [21].

Treatment options & service provision

Many allergic rhinitis sufferers have persistent symptoms that require pharmacotherapy. A recent systematic review of the randomized controlled trial literature of the effectiveness of commonly used pharmacological treatments in the management of people with hayfever recommended that non-sedating antihistamines and nasal corticosteroids should be first-line treatment options in those with mild-to-moderate disease [22]. Many studies have examined the sedative properties of antihistamines [23,24] and have shown significant sedative effects of first-generation antihistamines, but limited sedative effects of second-generation antihistamines. Despite current guidelines [3], many children in the case-control study referred to previously were taking sedating antihistamines at the time of their examinations. Adherence issues

are important as most treatments are given over long time periods and a failure to take treatments regularly may be central to why treatments often 'fail'. Allergen immunotherapy is an effective treatment option in those with more severe disease [25].

Treatments for hayfever aim to minimize or eliminate symptoms, optimize quality of life and reduce the risk of developing comorbidities. A report published in 2003, 'Allergy – the unmet need', commissioned by the Royal College of Physicians, clearly demonstrated current deficiencies in National Health Service allergy services in the UK in both primary and secondary care [26,27]. More recently, considerable variation in the awareness and management of allergic rhinitis was revealed in a survey of general practitioners, despite the fact that their practices had a self-declared interest in the management of allergic and respiratory disorders [28]. Under-diagnosis of allergic rhinitis remains a problem and the proportion of undiagnosed patients is as high as 60% [29]. Part of the problem appears to lie in the fact that many patients do not consult their general practitioner about their allergic rhinitis symptoms, and seek over-the-counter pharmacotherapy, while many may not recognize their symptoms as allergic rhinitis at all.

"...those who had hayfever symptoms on any examination day were more likely to drop a grade between their mock and final examination for maths, english and science..."

The House of Lords Science and Technology Committee report on Allergy (2006–2007) recommended that the Department for Children, Families and Schools should review the clinical care that children receive at school, and should reassess the way they are supported through the examination season [30]. However, it is important that primary healthcare professionals also have the necessary knowledge and skills to be able to manage patients with allergy symptoms effectively; there are now a number of pharmacological and educational interventions that have been shown to improve quality of life in allergic patients [31,32], and further work on educational interventions in teenagers is underway [33].

Should examination timetables be changed?

The current secondary school examination timetable combined with the application process for higher education is well established in the UK. Moving the examinations to the winter months may offset any potential disadvantage faced by adolescent hayfever sufferers, although this would have major knock-on implications for entry into higher education, which currently takes place after the summer break. There has been some discussion of post-qualification application to university [34], where students would sit their advanced ('A') levels/higher grades and obtain their results prior to an application for higher education, which may add more weight to the argument for earlier examination timings. The degree of cooperation between the education establishments required to coordinate such a radical change may well be prohibitive and, given that safe, effective and inexpensive treatments are available, could be considered unnecessary. However, consideration of the

evidence of the number of people affected by allergic rhinitis and its impact on their future should certainly be made in any future Department for Education and Skills curriculum reviews.

Conclusion

10 years ago, an editorial in *Paediatric Allergy and Immunology* posed the question of whether there was a case for unfair discrimination against hayfever sufferers sitting examinations in the summer [35]. This question is still relevant as we know that uncontrolled allergic rhinitis can significantly reduce quality of life and interfere with attendance through school absences. There is also a small but consistent body of evidence pointing to the fact that examination preparation and performance may be adversely affected by allergic rhinitis, particularly if patients are taking sedative medications. However, we also now know that it should be possible to achieve good symptom control with relatively simple medication regimens in the vast majority of young people. Delivering optimal care (defined pragmatically as timely and accurate diagnosis of hayfever and related comorbidities, education and empowerment of patients towards effective self-management, and appropriate pharmacotherapy) must then represent the mainstay approach to tackling the disadvantage that many young people

with hayfever currently experience. In those with resistant disease, there is also the need to consider hayfever as a mitigating factor, both in relation to examination preparation and when sitting examinations. In the longer term, we believe it would make sense to review the timing of examinations in any future major review of course and examination scheduling with a view to, if possible, moving these to the winter months.

Financial & competing interests disclosure

Victoria Hammersley is funded by the Scottish Chief Scientist Office as part of a Research Training Fellowship and is currently undertaking a trial exploring the effect of healthcare professional education on quality of life of adolescents with hayfever. Samantha Walker is Director of Education & Research at an educational charity that focuses on the education of health professionals as a key factor in improving patient health and quality of life. Aziz Sheikh has undertaken advisory work for a range of companies that manufacture diagnostic tests and pharmaceutical treatments for the management of seasonal allergic rhinitis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Appendix 15: Detailed costings for the trial

Scottish practice costs

Practice activity	Practitioner involved	Average time / cost per item	Hourly (or per item) rate (£)	Practice time for study / nos items	Total amount
Discuss study, read protocol, inform practice team	GP	1h	54	1	54
	Nurse	1h	23	1	23
	Practice manager	1h	20	1	20
Facilitate visit (from Study Manager)	Practice manager	1h	20	1	20
Search practice database	Practice manager	2h	20	2	40
Screen list of patients	GP	1h up to 200 patients; 2h up to 400 patients	54	1	54
Mailing to patients	Receptionist	2h up to 100 patients; 30 min extra per 100	11	2	22
Appts with 15 patients - approx 15 minutes per patient	Nurse	1h	23	4	92
Allocating appointments	Receptionist	2h per 100 patients	11	1	11
Answer patient queries	GP	1h	54	1	54
Postage		2nd class 27p letter 100g	0.27		0.00
		42p large letter 100g	0.42		0.00
Stationery		10p per invitation	0.1		0.00
Use of room		per hour	10		0
Per practice (£)					390.00

English practice costs

Practice activity	Practitioner involved	Average time / cost per item	Hourly (or per item) rate (£)	Practice time for study / nos items	Total amount
Discuss study, read protocol, inform practice team	GP	1h	77.18	1	77.18
	Nurse	1h	27.56	1	27.56
	Practice manager	1h	27.56	1	27.56
Facilitate visit (from Study Manager)	Practice manager	1h	27.56	1	27.56
Search practice database	Practice manager	2h	27.56	2	55.12
Screen list of patients	GP	1h up to 200 patients; 2h up to 400 patients	77.18	1	77.18
Mailing to patients	Receptionist	2h up to 100 patients; 30 min extra per 100	19.95	2	39.9
Appts with 10 patients - approx 15 minutes per patient	Nurse	0.25 per patient	27.56	4	110.24
Allocating appointments	Receptionist	2h per 100 patients	19.95	1	19.95
Answer patient queries	GP	1h	77.18	1	77.18
Postage		2nd class 27p letter 100g	0.27		0.00
		42p large letter 100g	0.42		0.00
Stationery		10p per invitation	0.1		0.00
Use of room		per hour	15		0
Per practice (£)					539.43